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Variations in Manifestations of Rheumatic Fever in Relation to Climate*

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THE statement can frequently be found in textbooks and monographs that rheumatic fever is ubiquitous. This generalization (which is often attributed to Hirsch[1]) can, however, scarcely be accepted today. Aside from the interest which has always been aroused by the seasonal incidence and familial occurrence of rheumatic fever, as well as the yearly variations in the severity of the disease, there has recently been some attempt to study, more accurately than has been possible before, the geographical distribution of the disease. The matter is one of importance not only in relation to rheumatic fever but in connection with other diseases. It is now well recognized, for instance, that infections such as scarlet fever and diphtheria, so common in the temperate zones, are almost unknown in some tropical countries. The geographical distribution of pernicious anemia, also, is very irregular. It is said to be almost unknown in China and Japan (Mills[2]).

My interest in possible climatological differences in the symptomatology of rheumatic fever was awakened, almost ten years ago, on coming to Baltimore from New York. Arthritis was often the predominant symptom of acute rheumatic fever in the adult in New York, and the one for which the patient called the physician or entered the hospital. Combined with the severe arthritis, or sometimes without severe arthritis, there was not infrequently observed acute, severe, and sometimes fatal endocarditis, pericarditis, myocarditis, pleurisy and pneumonia.

In Baltimore, on the other hand, the acute severe arthritis, so familiar in New York, was rarely encountered in the wards of the hospital. In general, though the disease seemed common in Baltimore, it presented a somewhat different clinical picture, appearing more insidious, less outspoken in its arthritic manifestations, not so fulminant in its severer forms, but suggesting usually a chronic or relapsing progressive disease of the heart. In order to obtain more definite information on these points, the case histories of patients with rheumatic fever treated during the last five years in the adult medical wards of the Johns Hopkins Hospital have been analysed.

*From the Medical Clinic, the School of Medicine, Johns Hopkins University and Hospital. Read at the Baltimore Meeting of the American College of Physicians, March 23, 1931.

It is difficult, as Newsholme[3], who was interested in this question, found many years ago, to obtain accurate information regarding the regional distribution of rheumatic fever throughout the world. The statistics collected from hospitals by Faulkner and White,[4] by Harrison and Levine,[5] and by Seegal and Seegal[6] indicate that rheumatic fever is commoner and more severe in the colder portions of the temperate zones than in the warmer portions. Seegal and Seegal also found that the incidence of rheumatic fever was greater from 1916 to 1918 than from 1918 to 1925. Excellent as these statistics are, they are based on diagnoses made in a variety of hospitals, and one cannot help but wonder upon what criteria the diagnoses were made. Do these statistics represent only those cases of rheumatic fever presenting arthritis, or do they include all cases of rheumatic fever? It is usually assumed that practically all cases of mitral stenosis are instances of rheumatic fever in the active, quiescent or healed stage of the disease. It is therefore very important in investigating the geographical distribution of rheumatic fever to know the regional distribution of mitral stenosis. Meleney and Kellers[7] state that though rheumatic arthritis is rare in China, mitral stenosis is common. Harrison and Levine found mitral stenosis frequent in Boston, St. Louis and Baltimore, much less frequent in Galveston, Richmond and Oklahoma, and rare in New Orleans. Wood, Jones and Kimbrough[8] find rheumatic fever and rheumatic heart disease about half as common in Virginia as in Massachusetts. Clarke[9] believes that rheumatic fever is almost unknown in natives in the tropics, defining the tropics as an area lying between 23° 28′ North and South. He states that he did not see a single case of rheumatic heart disease among 150,000 hospital cases in Perak, Malay States. Coburn[10] quotes Getz as stating that in the last 4 years only three unquestioned cases of rheumatic pancarditis have been recognized at autopsy at the Hospital of Santo Tomas in Panama. According to Coburn, rheumatic fever is extremely rare in Porto Rico. In about 500 autopsies studied by Dr. Lambert and Dr. Pappenheimer no gross or microscopic lesions of rheumatic fever were found. In a later series, however, two autopsies showing rheumatic pancarditis have been recorded.

The information, therefore, that is obtainable through published statistics and from such important personal surveys as that made by Coburn, goes to show that rheumatic fever, in all its forms, is exceedingly rare in the tropics, though rheumatic heart disease is not unknown in some tropical countries; whereas all the manifestations of rheumatic fever are common in the colder portions of the North and South temperate zones, where rheumatic arthritis is particularly prominent. In the intermediate and warmer regions of the temperate zones, rheumatic fever is certainly not recognized with as great frequency as it is in the colder regions. The geographical distribution, according to Coburn, corresponds to that of scarlet fever.

In analysing the cases at the Johns Hopkins Hospital, rheumatic fever has

been considered as a generalized disease, and consequently there have been included in this category all instances of chorea, of mitral stenosis, of rheumatic pancarditis and of rheumatic arthritis, whether they have been observed in the active, quiescent or possibly healed stages of the disease. In the majority of the cases there was some definite evidence of activity while the patient was under observation in the hospital wards. It may be seen from Table I that rheumatic fever is quite common in Baltimore, for 1.37 per cent of all patients admitted to the adult medical wards suffer from rheumatic fever. The cases of rheumatic fever, moreover, form a fair proportion of all autopsies, at least 1.66 per cent. The figures for the admission rate are a little higher than those given by Faulkner and White for the Peter Bent Brigham Hospital in Boston (Table II).

TABLE I
ADMISSION OF RHEUMATIC FEVER TO ADULT MEDICAL WARDS

Five Year Period—Sept. 1st, 1925 to Oct. 1st, 1930.

Total Admissions =	10,380
Rheumatic Fever =	142
Admission Rate =	1.37%
Total Autopsies 1908-1929 =	8,164
Total Rheumatic Carditis =	146
Per Cent Rheumatic Carditis =	1.6

Since 36 of the 146 autopsies showed rheumatic heart disease in acute or subacute form, it may be inferred that the disease may occur in Baltimore as an acute and severe infection. The total mortality for the 142 cases was 16.2 per cent. Table III shows the age incidence at the

TABLE II
REGIONAL DISTRIBUTION OF RHEUMATIC FEVER
(Modified from Faulkner and White)

PLACE	Av. Yearly Med. Admis.	Rheumat. F. Chorea	Per Cent
Johannesburg, S. Africa	2,936	169	5.8
Glasgow Royal Infirmary	2,655	126	4.74
Mt. Sinai, N. Y.	1,641	58	3.6
Royal Prince H., Australia	1,966	58	2.9
London Hospital	10,273	274	2.7
Univ. Hosp., Iowa	1,537	38	2.4
P.B.B. Hosp., Boston	2,480	31	1.3
J. H. Hosp., Baltimore	1,723	23	1.37
Univ. Hosp., Omaha	760	5	0.7
Barnes Hosp., St. Louis	1,358	6	0.47
Charity Hosp., New Orleans	5,349	28	0.4
Univ. Hosp., Atlanta, Ga.	2,500	2	0.08

TABLE III
142 CASES OF RHEUMATIC FEVER

Age	Total Cases	Auricular Fibrillation	Heart Block	Bacterial Endocarditis	Deaths
0-20	49	3	9	3	13
21-30	40	4	3	6	7
31-40	33	12	6	2	8
41-50	14	11	1		3
51+	6	6		1	2
Total	142	35	19	12	23
Per Cent		25.3	13.4	8.5	16.2

time of observation, the occurrence of auricular fibrillation, the incidence of prolonged A-V time and the number of cases complicated by bacterial endocarditis. It is interesting to note that the proportion of patients with auricular fibrillation increases with the increase in age, and that bacterial endocarditis usually occurs in the younger individuals. The percentage of 1st, 2nd and 3rd degree heart block is small, but this is no doubt due to the fact that single electrocardiographic records were made in many instances. The figures show that delay in A-V conduction is also commoner in the younger than in the older patients, associated in all probability with the greater activity of the rheumatic process in the younger patients.

Males and females were almost equally affected; many more instances of rheumatic fever occurred in the white than in the colored race (Table IV). A careful analysis of the histories of these 142 cases and the condition on admission to the hospital discloses some interesting facts. Table V records the frequency with which various manifestations of rheumatic fever occurred during the life of these patients before they were seen in the hospital. The past history shows that in 15 there was no history of any illness, simulating rheumatic fever, and in 27, or 19+ per cent, there was no history of any rheumatic manifestation other than tonsillitis. There was a history of some form of arthritis without a history of cardiac disease in 37 patients, or in only 26+ per cent. On the other hand, cardiac disease is found to be remarkably common. In 14 cases there was a history of cardiac disease alone, and in 73 patients, or over 50 per cent, a history of cardiac disease either alone or in combination with some other manifestation of rheumatic fever. It is thus obvious that even in the histories of these patients cardiac disease is an important feature.

When one analyses the condition of the patients on admission to the hospital, the importance of cardiac disease becomes even more impressive (Table VI). Of the 142 patients, only 6 were admitted with arthritis alone and one with chorea alone. Of the entire number, 58, or only about 40 per cent, suffered with arthritis on admission, or during their stay in the hospital; while 135, or over 95 per cent, were admitted with cardiac disease or showed evidence of cardiac disease while in the hospital.

TABLE IV
SEX AND COLOR
142 CASES OF RHEUMATIC FEVER

Male	73	Female	69
White	59	White	55
Colored	14	Colored	14

TABLE V
HISTORY OF PREVIOUS MANIFESTATIONS OF RHEUMATIC FEVER — 142 CASES

No arth., ton., chorea, card.	15	Cardiac alone	14
Tonsillitis alone	12	Arth. and cardiac	43
Chorea alone	5	Chorea and cardiac	5
Arthritis alone	34	Arth., chorea and cardiac	11
Arthritis and chorea	3		
Total arthritis, no cardiac	37	Total cardiac	73

TABLE VI
RHEUMATIC FEVER—142 CASES, CONDITION ON ADMISSION

Diagnosis	No.	Diagnosis	No.
Arthritis alone	6	Cardiac disease alone	80
Chorea alone	1	Arthritis and cardiac disease	49
Arthritis and chorea	0	Chorea and cardiac disease	3
		Arthritis, chorea and cardiac disease	3
Total arthritis	58	Total cardiac disease	135

The observations upon these patients in hospital show quite definitely that many of them, though they gave no history of cardiac disease and though they were ignorant of the fact that they had cardiac disease, had had, nevertheless, cardiac disease probably for some years.

The figures thus emphasize the fact that rheumatic fever, as we see it, is essentially a disease of the heart, which may be preceded or accompanied by arthritis, often mild in character, by chorea, by tonsillitis, or occasionally by pleurisy, pneumonia, subcutaneous nodules and skin eruptions. During the acute stages the disease may be very severe or even fatal. Acute pericarditis occurred in 9 cases, acute pleurisy in 2; subcutaneous fibroid nodules were found in only 3 cases. Though many of these patients have died during the healed stage of the disease from the effects of the cardiac lesions or from such complications as bacterial endocarditis, at least 9 of the 22 autopsies showed that death was associated with some form of acute rheumatic carditis. The analyses which Dr. Thayer[11] has made of the fatal cases of acute and subacute rheumatic fever show that fatalities during the acute and subacute stages of the disease are not very rare at the Johns Hopkins Hospital.

Table VII shows the forms of heart disease observed in the 135 cases. Almost all of these patients presented the signs of disease of the mitral valve. A comparatively large number also showed the signs of aortic insufficiency. In three cases the signs were those of aortic insufficiency alone, though it seems probable that mitral disease also existed in these cases. In a few instances myocarditis or chronic adhesive pericarditis was present without the signs of mitral disease.

TABLE VII
FORMS OF CARDIAC LESIONS
IN 142 CASES OF RHEUMATIC FEVER

Mitral stenosis and insufficiency	76
Mitral sten. and aortic insuff.	50
Aortic insufficiency	3
Myocarditis	3
Acute pericarditis	3
Total	135

DISCUSSION

In reviewing these histories of patients, many of whom I have studied in the wards, the fact becomes quite clear that rheumatic fever is practically as common in the hospitals of Baltimore as in the hospitals of Boston. The character of the disease is not precisely the same, for arthritis, in the severe form, is certainly not common in Baltimore, and arthritis, even in mild degree, occurs in only a moderate proportion of cases. Cardiac disease, on the other hand, is extremely common and has been present in 95 per cent of the cases that we have studied. Patients are not often

seen in the florid stage of the disease, though severe acute rheumatic pancarditis is by no means unknown. As compared with the incidence of cardiac disease in other series of cases of rheumatic fever, the figures at the Johns Hopkins Hospital are rather high. Mackie[12] states that serious cardiac disease occurred, irrespective of age, in 68.3 per cent of his series of 393 cases of rheumatic fever, and that between the ages of 10 and 15 approximately 78.2 per cent of all cases presented evidence of cardiac disease during the first attack. Poynton[13] found cardiac disease present in 70 per cent of 500 rheumatic children whom he examined. These figures are a high average for those found in the literature.[14] At the risk of redundancy, then, it may be repeated that rheumatic fever, as seen in Baltimore, is essentially rheumatic carditis often of insidious onset, with comparatively mild acute exacerbations, but progressing none the less to a chronic deforming endocarditis with involvement of the myocardium and often of the pericardium, and resulting eventually in chronic invalidism and death. The carditis may be preceded or accompanied by attacks of arthritis, usually mild in character or by chorea.

The predominance of carditis in rheumatic fever and the insignificance of arthritis as a feature of the disease has been observed elsewhere. Meleney and Kellers have called attention to the fact that mitral stenosis occurs only a little less frequently in Peiping, China, than at St. Bartholomew's Hospital in London, and yet rheumatic arthritis is almost unknown in Peiping or in North China. Coffen[15] points out that mitral disease is encountered in Oregon with a frequency entirely disproportionate to the number of cases of rheumatic arthritis, and Houston[16] in describing 88 cases of rheumatic fever which occurred during a period of four years amongst 115,213 general admissions to the Charity Hospital in New Orleans, emphasized the mild character of arthritic symptoms and the frequency with which cardiac disease occurred (51.1 per cent).

It seems possible, therefore, that rheumatic fever might be detected more frequently in the Southern States and in semi-tropical countries if the disease were regarded as one primarily of the heart, and if it were thoroughly appreciated that arthritis is an insignificant feature; an episode which may attract little attention or may be entirely absent.

Conclusions

The available statistics concerning the geographical distribution of rheumatic fever indicate that the disease is very rare or almost unknown in the tropics, and much less commonly observed in the warmer portions of the mid-temperate zones than in the colder portions.

In some regions where rheumatic arthritis is said to be rare, mitral stenosis is quite frequently observed.

At the Johns Hopkins Hospital in Baltimore the admission rate to the adult medical wards for rheumatic fever, in all its forms and in all its stages, over a period of five years was 1.37 per cent. The autopsy rate for rheumatic heart disease over a period of 21 years was 1.66 per cent. The disease, therefore, is comparatively common.

An analysis of 142 cases of rheumatic fever studied during this period

showed that symptoms or signs of cardiac disease appeared in the past histories of 50 per cent of the cases.

Cardiac disease was present on admission to the hospital or was detected during observation in hospital in 95 per cent of these cases. Only 6 of the entire 142 cases presented symptoms and signs of arthritis alone, but in 77+ per cent arthritis, often of mild degree, occurred at some time during the illness for which they were admitted to the hospital.

Rheumatic fever, as it is seen at the Johns Hopkins Hospital, is essentially a disease of the heart, frequently preceded or accompanied by arthritis, often of mild degree, or by chorea. Severe acute arthritis is rarely seen, but acute pericarditis and pleurisy are not very infrequent.

It is suggested that the infrequency of severe acute arthritis, the great frequency of carditis and the comparative insidiousness of the disease during the acute and subacute stages, renders the clinical picture of rheumatic fever somewhat different in Baltimore from that generally described for more northern sections of the United States.

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Colonic Changes in Chronic Arthritis*

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THE etiology and progress of changes in the colon so often noted in arthritis have been very great controversial points. Where many different opinions are held as to the cause of a condition and many methods of treatment advanced for the alleviation of the disease, it is evident a true understanding of the basic factors has not been reached. The roentgenological observations which we report here were noted on examination of patients suffering with chronic arthritis. The investigation was carried out by the permission of Professor Duncan Graham, and with the collaboration of Dr. A. A. Fletcher of the Department of Medicine. These observations have proved certain phases in the interpretation of the colonic disturbances, and we believe have an important bearing on the evolution of the disease.

Goldthwaite and Brown[1] pointed out the frequent observation of enteroptosis in patients suffering from chronic arthritis, and believed the enteroptosis to be either constitutional or acquired from faulty body mechanism. Assuming these premises to be correct, he and his co-workers treated many cases of arthritis by the application of belts, improvement of posture, and regulation of the function of the bowels.

Lane[2] defined stasis "as such a delay in some portion of the intestine, but more particularly the large bowel, as allows the absorption into the circulation of a larger quantity of toxic material than can be dealt with effectively". The delay, he remarked, is brought about by a mechanical alteration in the drainage apparatus. Among the many clinical manifestations due to colonic stasis, he particularly drew attention to arthritis. Lane stated that in early life colonic stasis is caused by abnormal distention of the bowel through too frequent feeding, or articles of diet of an unsuitable nature. Later in life it is brought about and accentuated by the erect posture of the body. He holds this posture causes a drag upon the principal points of support, tending to the promotion of bands and kinks at these points. These bands and kinks are evolutionary and not inflammatory. Proximal to these bands and kinks he states dilatation and stasis occurs.

Lane's theory of colonic stasis is combated by many observers. Bassler[3] believes these bands to be physiological and that sagging of the colon does not necessarily mean colonic stasis. Daniel[4] holds these bands to be

*Read at the Baltimore Meeting of the American College of Physicians, March 27, 1931.

due to a localized peritonitis. Keith[5] does not accept Lane's idea and denies that bands or kinks produce delay in the food stream. In defense of his statement he submits his own theory. He has noted in the myenteric plexus, or rather intermediate between the plexus and muscular fibres, certain cells partaking of the character of nerves and muscle. This he calls nodal tissue because of its close resemblance to the nodal tissue in the heart. His suggestion is that irregularities in impulse conduction may occur in the nodal system of the colon, and cause stasis as in heart block. We have also noted marked improvement in colonic tone during spinal anesthesia and following a section of the lumbar sympathetic branches.

Jordan[6] who long supported Lane stressed the roentgenological evidence of drags at the ligament of Treitz, kinks, and bands in the last part of the terminal ileum, the hepatic flexure, the splenic flexure and the sigmoid. These he states are evidenced by a constriction of the lumen of the bowel at the site of involvement, limitation of movement on forced inspiration, on palpation and with postural change. Jordan's investigation for years formed the ground-work for roentgenological study of the colon in colonic stasis and colonic dilatation.

Rae Smith[7] recently discussed the relation of the pathology of the right lower quadrant to arthritis, paying particular attention to the blue thin-walled toneless cecum, and has obtained relief following plastic operation upon the large bowel. He emphasizes the presence of constricting bands upon the ascending colon, believing the etiology of the constriction to be due to faulty fusion in the last stage of migration, rotation and descent of the colon. As a result of the faulty fusion we have a *cecum mobile* and an ascending colon possessing a mesentery. He states "Given this faulty fusion we have the stage set for a long chain of events. Starting with the loss of tone due to advancing years or a long strain due to illness, we have a loss of the lumbar curve, that is the shelf on which the cecum rests. With the loss of the curve the cecum tends to prolapse. In an effort to correct the position of the prolapsing cecum, nature starts the growth of a membrane at the site of the right colic artery on the mesentery side. This attaches the colon to the side wall by a reduplication of the peritoneum, the colon is rolled and twisted, pressure on the myenteric plexus results (here he evidently supports Keith's theory), a spasticity of the distal bowel results, with atony of the proximal portion, the cecum and the ascending colon."

Taylor[8] collaborating with Smith minutely describes the technique used in the roentgenological demonstration of these changes, and in an illuminating manner gives his interpretation of the screen and film findings. We are heartily in accord with Taylor's findings. On many occasions have we demonstrated the cecum low in the pelvis, atonic to bogginess, and on palpation have demonstrated a marked mobility raising the cecum at times to a point where it may be superimposed upon the splenic flexure. The deformity of the ascending colon also is often seen due to the membrane described by Smith, and the spastic distal

bowel is easily demonstrated. Occasionally at the six-hour examination the head of the meal will be present in the sigmoid, the colon from the site of the veil on the ascending colon to the sigmoid presenting the so-called "string type".

Our experience however has not allowed us to arrive at the same conclusions as Drs. Smith and Taylor. Of the large number of our cases giving the roentgenological findings described by them, very few indeed presented any evidence of arthritis, nor were we able to elicit a history of any attacks simulating that disease. On the other hand, in the many definite cases of arthritis that it has been our privilege to examine in collaboration with Dr. Fletcher, very few indeed have shown changes analogous with those observed by Dr. Taylor.

While it is the generally accepted theory that arthritis is as a rule secondary to some focal infection, the belief has been held to a degree that diet, or rather improper diet, has some relation to arthritis. Pemberton[9] advised diets low in calories and restricted in carbohydrates, and my colleague in this investigation, Dr. Fletcher,[10] has stressed the use of diets high in vitamins and low in carbohydrates.

McGarrison[11] in his work on animals showed that atony of the colon

FIG. 1

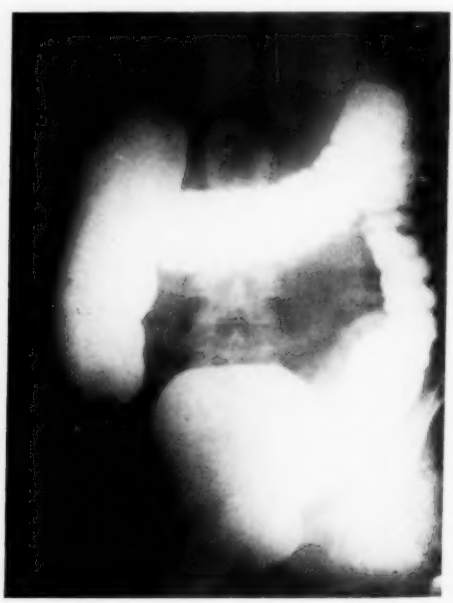

FIG. 2

FIGS. 1 and 2. Miss C., aged 17. Pain and swelling of the metacarpal joints for ten years. During summer of 1928 arthritis developed in knees, ankles, and shoulders. No history of sore throats and no focus of infection found. Admitted to hospital September 29, 1928, wtih moderately severe arthritis of rheumatoid type and also aortic mitral valve lesions with moderate cardiac hypertrophy. Changes are shown which occurred in the colon over six weeks of dietetic treatment. Marked improvement in the arthritis occurred during this time.

can be brought about by diets deficient in vitamin B, and suggests that the disturbance of mobility and tone in the lower bowel might be of nutritional origin. Using these results of McGarrison as a basis, we attempted to repeat his work, using white rats as our subjects and making our observations by the use of the barium enema.

Normal rats, well nourished and fed upon a diet rich in vitamin B, were given barium enemas. After this examination a diet deficient in vitamin B was exhibited for several weeks, when a second enema was given. The diet was again returned to one high in vitamin B and a third enema administered in a month's time.

The colon underwent marked changes during the observation. The second examination showed the bowel elongated and very atonic, so atonic in fact that the pressure from the flow of the enema was great enough to rupture the colon, and the enema poured out into the abdominal cavity. The rats we were fortunate enough not to lose by this accident were at once placed on a diet again rich in vitamin B and further observation made in a month's time.

At the third observation the tone of the bowel had returned to normal appearance, and it was much shortened in its total length. In some of the rats it was difficult to demonstrate any difference between appearances at the first and at the third enema.

FIG. 3

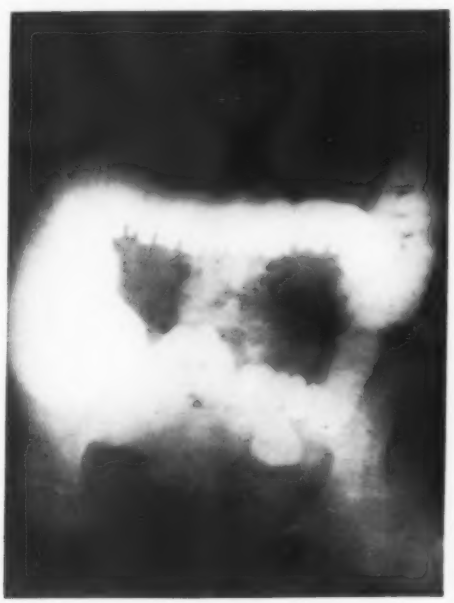

FIG. 4

FIGS. 3 and 4. Mrs. D., age 44. Moderate degree of osteoarthritis of three years duration. Blood pressure 178/108. Picture shows changes which appeared in the colon during two months of dietetic treatment. Well marked improvement took place while under this treatment.

With this point before us, it was assumed that some of the abdominal disturbances of chronic arthritis might be associated with nutritional deficiency, and at the request of Dr. Fletcher this investigation was undertaken in an attempt to prove or disprove the theory. Our first step was to demonstrate the incidence and type of colonic abnormalities in arthritic cases. When this had been done, we proceeded by periodical examinations, to demonstrate the effect of suitable diet upon the clinical progress, and the roentgenological appearance of the large bowel. In many cases the return to a normal appearance was indeed amazing. In others, and these were, we believe, complex cases, where nutrition alone played only a minimum part, the changes were slight or absent. It was, however, extremely interesting to note that in the majority of cases the improvement noted on the film bore a close relation to the improvement noted clinically. Latterly, we have been able with a very fair degree of accuracy, to state from the roentgenological examination, the amount of improvement, shown clinically, without any progress history being supplied from the clinician. Also, it has been possible after the first examination in some cases to give a prognosis pointing towards failure that has been borne out by the patient's subsequent course.

The roentgenological investigation may be carried out by use of the barium meal or the opaque enema. By the meal, the rate of progress or mobility will be demonstrated, and we must say we prefer the one-meal method to the two-meal one. In using the former, observations are made at the time of ingestion and at periods of six, ten, twenty-four, forty-eight, and seventy-two hours. If this is done a better understanding of the motility in each case will be obtained. The ten-hour observation is of great value. The head of the column has passed beyond the splenic flexure, the right lower quadrant is not obscured by coils of small bowel, and the appendix if filled is better seen and manipulated than at the six-hour observation.

In the vast majority of the arthritic cases examined, we saw no undue racing of the meal, the time of advance of the column's head being quite normal. In the cases showing hypermotility and spasticity, we were frequently able to demonstrate the constricted ascending colon due to a veil, and the markedly atonic cecum, but these cases indeed were few. The cecum was low in the pelvis, atonic in type, but not unduly free, demonstrating that no abnormal mesentery was present. The position of the ileocecal valve when demonstrated by an incompetency was normal, thus showing no rotation. The appendix when visualized, in very few of the cases was placed retrocecally, or in an abnormal position. The ascending colon appeared well filled, often longer than usually seen, no narrowing was observed, and the haustral markings were much decreased in depth. The transverse colon showed an increase in length, often festooned in type, the haustral markings poor, or entirely absent, and the so-called "H" formation was conspicuous by its absence. The descending colon shows a definite increase in length, varying from a slight

elongation to a marked redundancy, and reduplication with lessened haustral markings.

The enema gives much more evidence in our opinion than the meal, and in our re-examining of any case, the clysma is administered at intervals of about one month, comparing the various films at the completion of each examination.

Might we stress here the value of the fluoroscopic screen in conjunction with the film. During the flow of the clysma under the screen, the whole bowel may be palpated. The chance of not observing any evidence of narrowing, adhesions, veils or rotation, is to a great degree eliminated. Occasionally mass peristalsis will occur after the screen examination, and when the film is made the evidence has been obscured by this. The cecum will fill well, it will be placed low in the pelvis, and marked lack of tone is noted. The transverse diameter of the cecum will be increased, and the enlargement will be noted extending to a greater or less degree up the ascending colon. No narrowing of the ascending colon will be seen that may be due to a veil, nor do we see evidence of rotation.

The hepatic flexure as a rule may be noted about the level of the first lumbar vertebra, but occasionally in the very advanced cases it will be displaced downwards. When the transverse colon fills, it will be noted the haustral markings are lessened or absent, and the transverse diameter of the bowel is increased. The total length of the transverse is also greater than usually seen, and instead of the usual "H" appearance presented by the hepatic flexure, the transverse colon and the splenic flexure, the bowel has assumed an irregular festooned position across the abdomen. The splenic flexure is held in about its usual position, but in the more advanced cases, we have noted a downward displacement there.

The descending colon shows a redundancy in many cases, frequently complete reduplication of the bowel will be noted, and tone has become less, with haustral markings poor. In the cases showing extreme change, a complete disorientation of the colon is noted.

As mentioned above, re-examination has been carried out on a large number of these cases. These examinations are spaced about one month apart. The findings at these periods were in many cases very gratifying indeed. At these observations the cecum is held at a higher level in the pelvis, the transverse diameter is lessened, and haustral markings are returning. In some of the cases this is very marked. The ascending colon shows better haustration, and on measuring the longitudinal diameter of the cecum and ascending colon, we have noted a decrease of as much as two inches. The transverse colon presents a lessened transverse diameter, its total length is decreased, and the haustral markings are improved. This shortening of the ascending and transverse colon leads one to believe the longitudinal fibres play a definite part in the changes taking place. The festooning has disappeared, and a return toward the "H" type is noted.

The descending colon presents its changes also. The reduplication will be noted to have lessened in extent,

tone has improved, and haustration is better. The appearance present throughout the whole colon is that of increasing tone, returning to or at least approaching the appearance of a normal tonic colon.

In reviewing the cases examined, of which we now have about two hundred in the department, the changes mentioned above were present in 66 per cent, and improvement was present in a great majority. Coincident with the improvement of the roentgenological appearance, the clinical picture also gives a definite change for the better, reaching in some a complete amelioration of the symptoms.

All of these cases have been observed under careful control. Some had been confined to bed for many months, previous to the institution of treatment. One or two were not confined to bed at any time during the investigation. At the time that dietetic treatment was undertaken all other remedial measures were discontinued, or had never been instituted.

From the foregoing observations, there seems to be no doubt that tone and motility of the large bowel are dependent on the nature of the diet, and in cases of atony definite improvement may be expected by these dietetic measures. Further, the improvement in the general condition of the patient and the amelioration of the

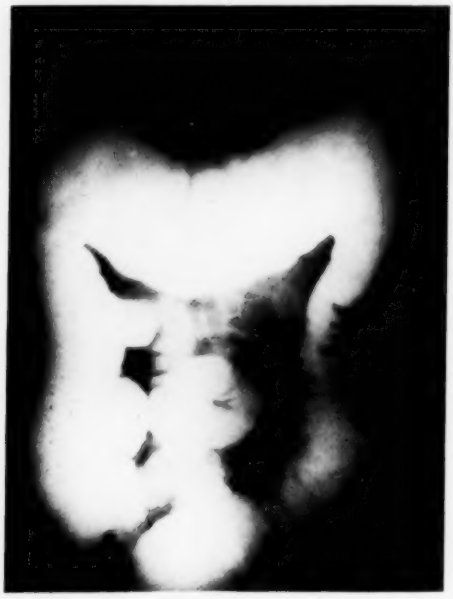

FIG. 5

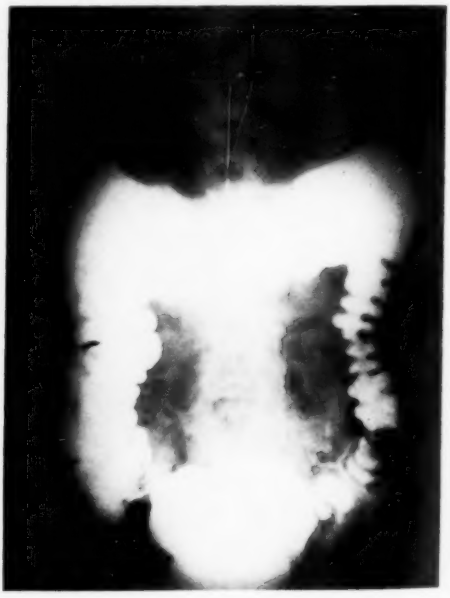

FIG. 6

FIGS. 5 and 6. N. B., aged 26. Rheumatoid arthritis started in 1922. Some improvement in 1924 following tonsillectomy. Later disease became more severe and from 1926 was confined to bed. Admitted May 28, 1928, showing advanced fibrous change in knees and ankles, ankylosis of hips and atrophy of muscles and bone. No further focus of infection found. The changes shown above occurred during four months of dietetic treatment. There has been slow but continued clinical improvement during the course of dietetic treatment.

symptoms coincident with the changes demonstrated by the roentgenological observation, leads us to believe that malnutrition is playing a part in the clinical picture of arthritis, and those atonic changes are a definite expression of the malnutrition.

These investigations have been carried out upon patients with rheumatoid-arthritis and osteoarthritis, and the colonic changes above described have been present in both types. The rheumatoid-arthritic group has shown the greater colonic changes and the more improvement under dietetic treatment. We do not wish to create the impression that we consider the colonic changes described above as the primary abnormality, rather they are indicative of some other pathological process of more importance, due to nutritional deficiency, which is an important factor in the evolution of arthritis.

Dr. Fletcher has followed two general principles in his dietary treatment of these cases. First the liberal ad-

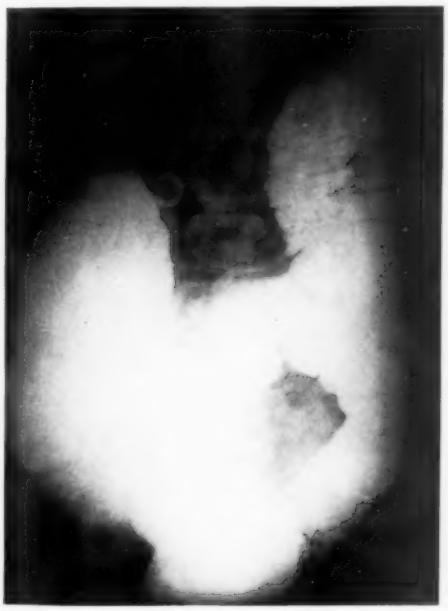

FIG. 7

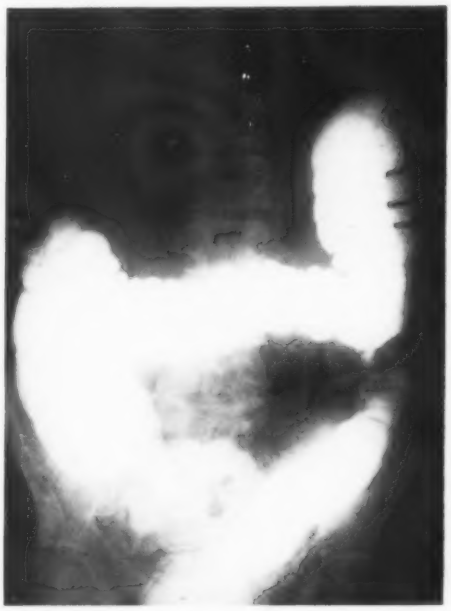

FIG. 8

FIGS. 7 and 8. A. E., was in the hospital from Dec. 3, 1930, to Feb. 28, 1931. Five or six years ago patient began to develop pain and swelling of various joints of body with some limitation of movement. Four years ago had developed marked limitation of movement of right shoulder-joint following radical breast amputation (for scirrhous carcinoma). Arthritic involvement was in right elbow first, then left wrist, right wrist, both knees and ankles, and then left shoulder. More recently within last 2 years both hands have been involved. (small joints). Shortly after onset of joint pains had teeth and tonsils removed. Three weeks before admission patient first noticed swelling over sternum which was prominent (at right sterno-clavicular joint) on admission. Skin over it slightly reddened and tender. This swelling largely subsided in hospital and there was moderate improvement in other joints. Marked improvement in arthritis during residence in hospital, and definite improvement in colon as shown in the films.

ministration of vitamins, especially vitamin B; secondly, a change in the balance of diet. He gives liberally food high in vitamins such as fresh vegetables and fruits, cream, butter, eggs and liver, and vitamin B is increased by administration of baker's or brewer's yeast or wheat germ. The last appears the more effective upon these disturbances of the colon. Fifty to sixty grams of protein are given in the form of meat, fish, eggs, or liver. Fat is exhibited according to the patient's caloric requirements.

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Total Occlusion of the Right Branch of the Pulmonary Artery By An Organized Thrombus*†

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THE following case, because of the apparent rarity of one of the lesions found, total thrombotic occlusion of a main branch of the pulmonary artery, and the interest of its physiological connotations, is considered worth reporting.

The existing literature contains but few cases of such occlusion of a main branch, although multiple thromboses of the smaller arteries appear fairly common. A case of that sort has recently been reported by Frothingham.[1] A monographic article by Posselt[2] in 1909 reviews thoroughly all types of pulmonary artery disease, and may be considered to cover the literature up to that time. He was able to find only three cases of complete occlusion of the pulmonary artery or one of the major branches.

The first was that of von Jürgensen. It may be summarized as follows:

The patient was a male, sixty years of age, who had had dyspnea for several years which had become distinctly troublesome during the last six weeks. Physical examination showed dyspnea and marked cyanosis; respirations 40, pulse 88, beat irregular and distinctly intermittent. The lungs were emphysematous. The heart was enlarged to percussion, especially to the right. The sounds were all weak, but the pulmonic seemed especially weak in comparison with the aortic. There was sclerosis of the peripheral arteries. The day after entry he had a sudden slight hemiplegia with left facial paralysis and difficulty in speech. During the following two days indefinite pulmonary signs developed which were associated with a bloody sputum and it was thought he probably had pneumonia. On the third day he suddenly developed convulsions and died.

Autopsy showed the main trunk of the pulmonary artery completely occluded by a pale, reddish-gray thrombus, one inch in length, which was loosely but definitely adherent to the wall. Attached to it were several smaller, redder and fresher looking thrombotic masses. They were less adherent than the large, grayish mass. The right pulmonary artery also contained a completely occluding older thrombus, which was also adherent. The vessels in the region of the thrombi showed patches of atheroma. The heart was enlarged with hypertrophy of both ventricles. Thrombi were present between the columnae carneae in the right ventricle. The valves showed no abnormality. The lungs showed interspersed areas of emphysema and collapse. A few small infarcts were present. An acute miliary tuberculosis was found with tubercles in the lungs, liver, kidneys and retroperitoneal glands. No mention of hypertrophy of the bronchial arteries is made,

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though von Jürgensen assumes in his discussion that the lungs must have been nourished in this way.

Posselt also found two cases reported by Hart. They were in brief as follows:

Case I: A woman with signs and symptoms of heart disease consisting of a mitral systolic murmur, dyspnea and cyanosis, particularly of the fingertips, died under observation in the hospital with symptoms of gradually increasing decompensation.

The autopsy showed marked cardiac hypertrophy of both the left and right sides of the heart. There was a well marked mitral stenosis with a fresh verrucose endocarditis. A thrombus was found in the pulmonary artery which completely occluded the main stem and the right primary branch and partially occluded the left primary branch. It showed definite lamellation and evidently had been deposited in layers. There was well marked organization at the periphery. The lungs showed extensive pleural adhesions. They were normal in volume, only slightly increased in consistency, crepitant throughout, and very rich in blood.

Case II: A man with symptoms of tabes dorsalis of five years' duration developed a pyelonephritis. Three weeks before death he developed what was apparently a slight bronchitis but associated with it was a marked impairment of his general condition ("Störung des Allgemeinbefindungs").

At autopsy a pale, grayish-red thrombus with indistinct lamellation was found which completely occluded the main stem and the right primary branch and partially occluded the left branch. There was no cardiac hypertrophy. The lungs were of normal volume, air-containing throughout and hyperemic. In the iliac vein an older, totally occluding thrombus was found. Microscopic examination confirmed the organization at the periphery of the lungs in both cases. In neither case was an increase in diameter of the bronchial artery demonstrated.

Barnes and Yater[3] in 1929 reported a case of thrombosis of the large pulmonary arteries.

A man of 34, was seen first in August, 1926, when he complained of dysphagia and vomiting associated with marked dyspnea on effort. Fifteen months previously he had had a septicemia following a hand infection, and four months previously a sudden attack of pain in the left chest, worse on deep breathing, and a week later similar pain on the right. Examination revealed no adequate explanation of these complaints. A positive Wassermann was found and antiluetic treatment was given. He gradually improved and got back to work. In the autumn of 1926 there was some suggestion of lung abscess, but this did not persist.

On re-examination in March and October, 1927, and March, 1928, there was found evidence of congestive heart failure, marked cardiac hypertrophy and gallop rhythm. The pulmonic second sound was greatly accentuated and the electrocardiogram showed right ventricular preponderance. He gradually became more and more dyspneic and edematous and died of progressive cardiac failure in September, 1928. In the late stages of his illness he developed an erythrocytosis.

The significant autopsy findings were old thrombi in the main trunk of both pulmonary arteries and hypertrophy of the right ventricle. The thrombi were dense, white masses, about 4 cm. long and 0.5 cm.-1.0 cm. in diameter, in the pulmonary arteries between the main trunk and the subdivision of the arteries into their branches. These thrombi greatly reduced the lumina of the arteries, the right more than the left. They were firmly adherent to the walls. The arteries were not sclerotic and appeared to be dilated. The heart valves were normal except for the mitral, which showed some verrucose, rheumatic endocarditis. The coronaries were not sclerosed but appeared dilated. Some chronic adhesive pleuritis (bilateral) and pericarditis were found, also bronchiectasis with abscess-formation in the base of the upper right lobe. Grossly the lungs showed little other evidence of disease.

The authors comment on the unusual problem in diagnosing serious heart failure without obvious expla-

nation. There had been no evidence of valvular, hypertensive, or coronary disease. The cardiographic findings and the loud pulmonic second sound led to a diagnosis of cardiac failure, chiefly of the right heart, due to some obstruction in the pulmonary circuit. The finding of the pulmonary thrombosis made it clear that the history of seizures of pain in the chest with dyspnea denoted embolism. The obstruction of the pulmonary circulation by the subsequent thrombosis threw extra work on the right heart and caused failure.

Jump and Baumann[4] have also published a case of pulmonary artery thrombosis with chronic cyanosis and polycythemia.

A man of 48 was admitted to the Philadelphia General Hospital complaining of swelling of the legs of two weeks' duration. He had also more recently had dyspnea and palpitation on effort. On examination he showed slight edema and very marked cyanosis of the face, especially dark around the nose and lips. There was also moderate cyanosis of the extremities. The heart was not enlarged and there was a soft systolic blow at the apex, not transmitted. The liver was palpable 5 cm. below the costal margin. The pulse ranged from 60 to 80 and the red blood cell count varied from 5,200,000 to 7,700,000. The blood pressure was 130/80. The electrocardiogram showed right ventricular preponderance. After two months in a stationary state, except for gradually increasing cyanosis, he died with signs of right heart failure.

The autopsy showed right ventricular hypertrophy and dilatation. The pulmonary artery was dilated. About two inches from the orifice was a large thrombus attached to the posterior wall and extending into both branches. The left side of the heart was not remarkable; the valves were normal. The left lung was voluminous, markedly congested and dark purplish-red in color. Section of the pulmonary artery showed considerable thrombotic material firmly attached to the walls and extending to the smaller subdivisions. The thrombus was large enough almost to occlude the vessel. Underlying it there was some arteriosclerosis. The right lung was congested and also showed some tuberculosis. The right branch of the pulmonary artery showed the same changes as the left, i.e., marked thrombosis and moderate arteriosclerosis. The liver and spleen showed chronic passive congestion. The first portion of the aorta showed moderate arteriosclerosis. Jump and Baumann point out a close resemblance between the symptomatology in their case and that of so-called Ayerza's disease.

More recently Brenner[5] has reported six cases in which were found thromboses of large branches (not main branches) of the pulmonary artery. In all but one there was microscopic evidence of organization of the thrombi. This author concludes that the thrombosis usually occurs after severe congestive failure has set in and produces no evident additional symptoms, though it probably hastens the end.

Our own case is as follows:

Case Report

An American business man of 60 entered the private ward of the Massachusetts General Hospital as the patient of one of us (J. H. M.) on November 11, 1929, obviously in a terminal stage of congestive heart failure.

No history of rheumatic disease could be obtained and it was quite certain that he had never had syphilis. He had for some years been a patient of Dr. James B. Herrick of Chicago, to whom we are indebted for considerable information. Among other things Dr. Herrick wrote us the following:

"He came to me first in 1905 for a trouble entirely unrelated to his heart..... At that time I recorded an aortic regurgitant murmur. I did not see him again for ten or twelve years but have seen him off and on several times since. Two or three times

he was laid up with an attack of renal colic with marked hematuria. The X-ray showed stone. Both Dean Lewis and I felt in view of his heart condition and the comparative harmlessness of the stone in the kidney that an operation should not be done."

In 1922 he had an operation upon his thyroid by Dr. J. M. T. Finney of Baltimore. He had had a goiter for several years and it was apparently a familial affair occurring also in three or four of his immediate relatives. Dr. Finney wrote to us as follows: "He presented himself to me in the summer of 1922 with large, toxic, multiple adenomata of the thyroid. He was suffering from pressure on the trachea, as well as from toxemia.

"Although he was not a good risk, I advised operation, which was done in June, 1922. The thyroid proper was pretty well displaced by several large adenomata, which involved pretty much the whole gland. They were partly sub-sternal and partly above, displacing the trachea quite markedly. Operation was made more difficult on account of free bleeding from the large vessels, as well as from the size of the gland, and from the fact that a large adenoma was retro-sternal and could be delivered with difficulty. Only a small portion of the glandular tissue was left; that was posterior, and was thought to be sufficient to provide function as well as to insure no injury to the parathyroids." He made a satisfactory recovery, and some dyspnea which had been present before operation disappeared. In fact he became wonderfully well.

In other respects the past and family stories seemed unimportant.

The symptoms which led up to his final illness began in September, 1928, with slight dyspnea on effort. This was relieved for a time by digitalis. In November, 1928, according to Dr. Herrick, "he had an acute and very violent respiratory tract infection, resembling in every respect the influenza we had in 1918. His temperature was about 105°. He had no leucocytosis. There was definite consolidation in patches. He became extremely cyanotic and orthopneic and it looked as though he were going to die. He was pretty heavily digitalized and he pulled through."

He made some improvement after the infection, but was never really well again. In January, 1929, he got to Florida, but the trip tired him so bady that he led a bed or wheel chair existence there. He was having definite cardiac symptoms, dyspnea, and edema of ankles. In March he was moved to Atlantic City where he stayed in bed for two months on digitalis, with a slow and gradual improvement. During this time he had several nosebleeds. In May he went to his summer home in Vermont. After arriving there he stayed in bed for two weeks on digitalis and a restricted diet. By the middle of June he was much better; he could lie flat, breathe fairly well and walk slowly about the garden.

This improvement was maintained until the beginning of October, when his dyspnea and edema of his lower extremities returned, gradually increasing in degree. From October 10 on he had orthopnea and during the two weeks or so prior to entry, gradually increasing cyanosis. He had had practically no cough or sputum and no pain in the chest or palpitation. There had been some attacks of restlessness at night, but no sudden dyspnea, choking or wheezing. No headache, visual disturbance, nausea or vomiting had been present. There had been considerable heartburn. He had had nocturia, once per night, during the summer, with apparently a fairly normal total output of urine.

As he was steadily getting worse it was decided to transfer him to the Massachusetts General Hospital.

On arrival (November 11), after an one hundred and fifty mile motor ride, which he stood surprisingly well, examination showed him to be a cyanotic, orthopneic man with Cheyne-Stokes breathing and pin point pupils (morphine). The cyanosis was of medium intensity and generalized. The heart was enormous, the left border being in the mid-axillary line and there was a heaving impulse over a wide area in the sixth and seventh interspaces. No enlargement to the right was made out, nor any increase in supracardiac dullness. There was a loud, double murmur audible over the entire precordium and outward along the clavicles and, to a slight extent, up into the neck.

This double murmur was most loudly heard in the aortic area. At the apex there were three blowing murmurs giving a gallop sound. The only normal heart sound heard was a rather weak P_2. No friction or thrills were made out. The rate was 82 and the rhythm regular. The blood pressure varied from 140 to 170 systolic over 20 diastolic. The neck veins were somewhat engorged.

The lungs were surprisingly clear. There was good resonance throughout with normal breath sounds. There were a few crackles at each base. The abdomen was slightly distended, but otherwise negative. The liver was not felt. There was moderate, soft edema of both lower legs, lower back and inner aspects of the thighs, but not of the scrotum. In all other respects the physical examination seemed unimportant. The scar of thyroidectomy was noted in the neck, but no evidence of thyroid tissue was discovered.

In hospital through November 13 his condition remained critical but without important change. Digitalization was maintained and in addition theocine was given. No diuresis was produced. The outstanding difficulties were the respiratory distress and cyanosis, and yet no physical signs of importance could be discovered in the lungs.

On November 14, after large doses of caffeine, the Cheyne-Stokes breathing gave way to an equally distressing type of regular breathing. On that day there was noted some edema of the left arm, and the temperature which had been subnormal until then, rose to 103°F. He gradually sank into a stupor; the breathing became very jerky and on the morning of November 15 he died. The pulse rate of 100 at entry rose to 120 the morning of his death.

The laboratory work obtained during this brief stay in hospital was as follows. Four examinations of the urine showed specific gravities of 1.020 to 1.030, a large trace of albumin in all specimens, sugar in none. The urines were all acid and cloudy and the sediments all showed red blood cells, white blood cells, and many hyaline casts. The white blood cell count on November 12 was 19,700 and on the 14th, 17,000. The nonprotein nitrogen of the blood on November 12 was 66 mg. per 100 c.c. The Hinton test on the blood was negative. The electrocardiogram showed a regular rhythm, rate 100, with slurred QRS in all leads, moderate left axis deviation, intraventricular block, probably right bundle branch type; also auricular-ventricular block and upright T_1 and T_2 and diphasic T_3.

The *clinical diagnosis* was arteriosclerotic and hypertensive heart disease with dilatation and marked hypertrophy of the heart, aortic valve disease with regurgitation, congestive failure, chronic passive congestion, and terminal bronchopneumonia. The last was by inference only since no physical signs of pneumonia had been found. The nature of the aortic lesion was thought to be arteriosclerotic, since no evidence whatever of either syphilis or rheumatic infection had been obtained. This note was also made before death, "The deep cyanosis would suggest some factor in the lesser circulation but the lungs are surprisingly clear, showing only a few unimportant crackles at the base." Congestive failure was regarded as the chief cause of death with bronchopneumonia a contributory cause.

The *post mortem examination* showed a remarkable variety of unusual lesions. The most striking was a complete thrombotic occlusion of the right pulmonary artery. Beginning exactly at the bifurcation the artery was completely filled by a reddish-gray, somewhat friable, adherent mass which extended about a centimeter into each of the three main branches of the artery within the hilus of the lung. There was no evidence either grossly or microscopically of canalization, but the character of the clot and its degree of organization at the periphery suggested that it must have been pres-

ent weeks or possibly months. The right lung, however, showed no trace of necrosis or of scarring. It contained much less blood than the left lung, which presented the usual picture of chronic passive congestion. It was smaller and slightly less crepitant than the left, yet it contained air throughout all portions and showed no evidence of collapse.

The absence of necrosis could of course be explained only by the development of a compensatory circulation. Evidence of this was readily found. Three arteries of unusual size led into the hilus region. The first was evidently a greatly hypertrophied bronchial artery, estimated to be four times the diameter of the normal bronchial artery. Two other vessels of unusual size compared with control specimens, ran along the sides of the

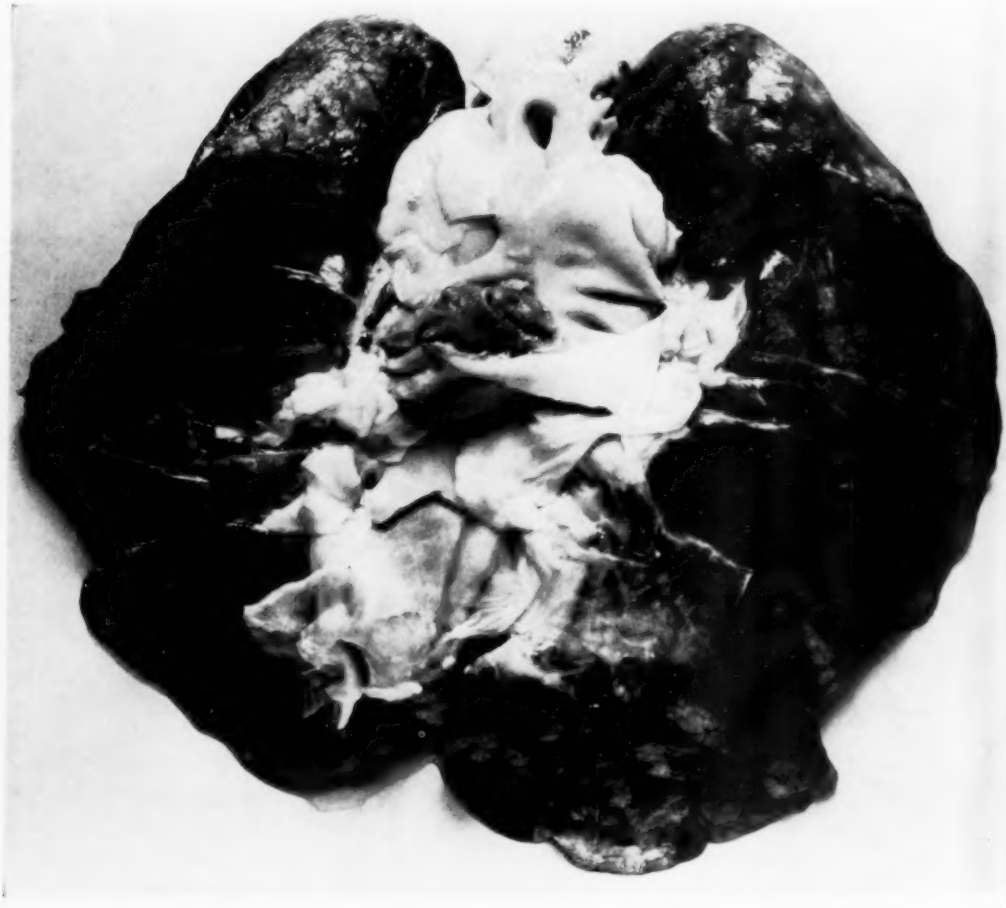

FIG. 1. Anterior view of the lungs one-third the original size. The right pulmonary artery has been opened to show a completely occluding thrombus, which on microscopic examination showed early organization at its periphery. The right lung is slightly smaller than the left but shows no infarction.

trachea anastomosing at their lower ends with the hypertrophied bronchial artery, and passing into the right hilus. They were traced upwards into the neck where they probably arose from the inferior thyroid arteries which supply the trachea, though the dissection was not carried high enough to demonstrate their origin.

Further examination of the right lung revealed several other findings of interest. In the region of the hilus was an irregular, pyramidal, calcified and partially ossified mass approximately 3 by 3 by 2 cm. It completely surrounded the primary bronchial branches which passed unobstructed through the area, though their walls were calcified. It also surrounded the first branches of the pulmonary artery which passed through the area without narrowing of their lumina. They were, however, occluded by thrombi continuous with the large thrombus in the main artery, but in this region the clot was redder, softer, less adherent and apparently of more recent origin. Microscopic examination of this region showed a mass of almost acellular, hyalinized and partially calcified, fibrous tissue in which were numerous foci of ossification containing well differentiated bone trabeculae separated by fatty and, in places, hematopoietic marrow. No foci of caseation and no areas suggestive of tuberculosis could be identified.

The pulmonary arteries beyond the point of thrombosis were entirely normal in appearance until the peripheral portion of the lung was reached, where many were found partially or completely occluded by fibrous plugs typical in appearance of completely organized thrombi. Many of these showed canalization. It is particularly interesting that exactly similar lesions were found in corresponding peripheral portions of the left lung.

The capillaries of the alveolar walls were difficult to make out, and very few red blood cells were found in the septa. The lumina of the alveoli, which in the congested left lung contained hemosiderin-filled "heart lesion cells", serum and occasional red blood cells, were for the most part empty or contained a mucoid secretion. The epithelium of many of the alveolar sacs showed a metaplasia into a high cuboidal or even low columnar type.

The other finding of greatest importance was in the heart. It was greatly hypertrophied, weighing 995 gm. The hypertrophy was shared between the two ventricles, both of which were greatly dilated, their walls hypertrophied. The right ventricle was proportionately slightly more hypertrophied, its walls measuring 7 mm. in thickness, whereas the left measured 16 mm. Both auricles showed moderate dilatation. The aortic valve was bicuspid—evidently a congenital lesion. It also showed marked calcification of both its cusps so that they were practically immobile and fixed in a position to cause both stenosis and regurgitation. The other valves were negative and the coronaries showed only occasional patches of atheroma without narrowing of the lumina.

A substernal colloid goiter weighing 75 gm. and a smaller separate one weighing 5 gm. were found in the anterior mediastinum above and anterior to the great vessels. It was not felt that they played a part in the symp-

FIG. 2. The hilus of the lung viewed from behind with the trachea and primary bronchi laid open. The aorta has been dissected free and reflected laterally to show the greatly hypertrophied bronchial artery passing behind the hilus glands.

tomatology. An incidental finding was a calculus in the right renal pelvis with an adjacent papilloma of the epithelium.

Discussion

The variety of unusual lesions found in this patient makes attempts at interpretation of their interrelations both interesting and baffling. Congenital bicuspid valves are ordinarily competent and the stenosis and regurgitation, evidence of which was noted first at the age of thirty-six, must be considered an acquired lesion. Syphilis was readily ruled out by the serologic studies in life and by the autopsy findings. The process might have been either rheumatic or arteriosclerotic in origin, the latter seeming to us more consistent with the anatomic findings, with the absence of mitral involvement, the late onset, and the lack of history of rheumatic fever.

The renal stone was evidently a side issue and the goiter, past history with no probable bearing upon the present illness.

The complete plugging of the pulmonary artery without necrosis, with the probable duration of life of weeks to months since its occurrence struck us as quite remarkable. Two possibilities came up for consideration, the local formation of the thrombus, or an embolus from some undetermined source. Local thrombus formation almost always presupposes local vascular injury. It was not thought that the calcified mass in the hilus of the lung could have been responsible, for although it completely surrounded the chief branches of the artery, it did not narrow them and their inner surfaces were in no way involved. On the other hand it seemed fair to assume that an embolus could not have been totally occluding from the start since so sudden a strain upon an already damaged heart would almost certainly have been immediately fatal, or would have produced clinical symptoms of which we have no suggestion in the history. A medium sized embolus might well have lodged in the right pulmonary artery producing at first only a partial occlusion, but gradually growing by accretion into a mass which completely filled the artery. This would have allowed time for the development of the rich compensatory circulation supplied by the hypertrophied bronchial artery and the anastomosing tracheal branches. The numerous partially or completely obliterated branches of the pulmonary artery found in the peripheral portions of both lungs might be the result of a shower of minor emboli which had been completely organized and partially canalized.

The case is interesting from the point of view of morbid physiology in that it proves that an entire lung may be separated from its pulmonary artery supply and suffer no injury of any sort provided the occlusion is gradual, allowing time for the establishment of a collateral circulation from the aorta. The situation reminds one of those cases of chronic total occlusion of both coronaries without history of the characteristic picture of coronary occlusion. The effect of slow closure of the pulmonary artery is evidently different from sudden shutting off, as from embolism or ligation, in which cases the picture of infarction is produced. Sauerbruch

and Bruns[6] experimentally found that even a main branch could be tied without disastrous consequences, but that fibrosis and shrinkage of the lung developed forthwith. They also have shown that in man in cases of bronchiectasis and tumors there is produced a marked shrinkage of the lung. Lilienthal[7] describes one ligation of the left main branch within the pericardium for abscess. The patient survived the ligation but soon afterwards drowned in pus from the abscess.

With regard to the collateral bronchial arterial circulation the work of Holman and Mathes[8] is of interest. These investigators found marked dilatation of the bronchial artery supplying a lobe containing an experimentally produced abscess.

From the clinical point of view it is of interest that such a gross disturbance in lung circulation can exist without altered physical signs in the lung. Since there was neither collapse nor edema, there was nothing to alter the percussion note or change the fremitus or breath sounds.

The thrombosis undoubtedly explains the cyanosis, for which no adequate explanation had been found during life, but which was thought to point to a lesion in the pulmonary circuit. Deep cyanosis is characteristic of other pulmonary artery diseases, so-called Ayerza's disease, for example, and is probably to be explained on the basis of diminished aerating surface to which blood can be exposed with consequent greater reduction of hemoglobin in passage through the lungs.

To what extent the thrombus contributed to the heart failure is impossible to say. The patient was entitled to die of congestive heart failure without it. Our guess, however, is that it probably importantly accelerated the failure. The hypertrophy of the right ventricle would substantiate this view. The thrombus could do this both by increasing the anoxemia, as well as by producing pulmonary hypertension by diminishing the total diameter of the pulmonary arterial tree. This seems to have happened in the patient of Barnes and Yater and also in that of Jump and Baumann.

Conclusions

Total thrombotic occlusion of a main branch of the pulmonary artery may occur without damage to the lung provided it develops slowly enough to allow for the development of collateral circulation through the bronchial system.

Such a lesion may produce no local signs in the lungs but the presence of cyanosis and right-sided heart failure without other obvious cause may suggest its presence.

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The Therapeutic Use of Oxygen in Heart Disease*

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Introduction

OXYGEN is the fundamental requirement for the transformation of energy in the body. A normal supply of oxygen to the tissues in an individual living at sea level atmospheric pressure is maintained essentially by intact respiratory and cardiac systems. Although the metabolism is not altered by an increase in the oxygen supply (Voit,[1] Pfluger,[2] and Benedict and Higgins,[3]) reduction in the normal amount of oxygen furnished to the tissues results in profound alterations in the chemical processes of the body. A state of oxygen-want or anoxemia may be produced by a diminished concentration of oxygen in the outside air or through an impairment of the respiratory or cardiac systems.

History

The direct effects of oxygen-want have been observed by many physiologists, either through studies at high altitude or through experiments in chambers in which the partial pressure of oxygen is lowered. Headache, nausea, and vomiting, irrational states and mental depression are common symptoms. The pulse is invariably elevated. The respiration is frequently periodic in character, changing to rapid and shallow breathing. In abrupt and severe want of oxygen, delirium, coma and cardiac failure occur. (Haldane,[4] Bancroft[5]).

Von Terray[6] found, as a result of the production of severe anoxemia, an increase in the excretion of carbon dioxide, increased elimination of nitrogen and a marked production of organic acids. Schneider, Truesdell and Clarke[7] also observed an increased elimination of carbon dioxide in periods of anoxemia which was immediately reduced by the inhalation of oxygen. Krogh[8] reported a decrease in the rate of oxidation when the oxygen supply to the tissues was diminished beyond a certain point, namely, when the oxygen pressure in the inspired air fell below 83 mm., or atmospheric pressure of 410 mm.

The rôle of oxygen-want in the production of the symptoms of heart disease has not been clearly understood. Previous studies bearing on this factor will now be referred to. Means and Newburgh[9] found a diminished oxygen saturation of the venous blood in cases of cardiac decompensation. These results were confirmed and amplified by Lundsgaard[10]. Harrop[11] showed that a diminished arterial oxygen saturation was present in cases of cardiac insufficiency. Barach and Woodwell[12] administered 40 to 60 per cent oxygen over short periods of time and observed that an increase in both the arterial and venous oxygen saturations occurred. When the arterial anoxemia was due to passive congestion and edema of the bases of the lungs, oxygen treatment regularly raised the arterial saturation to the normal level. The elevation of the venous saturation seemed largely dependent upon the increase of the arterial oxygen saturation. Diminution of

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cyanosis and slowing of the pulse were the outstanding objective changes. There was in some cases an increase in carbon dioxide content of the arterial and venous blood. In two cases of right bundle branch block, a decreased notching and a diminished height of the R wave were present during the inhalation of oxygen.

Beddard and Pembrey[13] found the carbon dioxide of the alveolar air reduced in cases of cardiac decompensation. This was confirmed by Fitzgerald[14] and later by Porges, Leimdorfer and Markovici[15] who observed that the alveolar carbon dioxide was low in cases of cardiac disease in whom dyspnea was present and normal in those without dyspnea. Peabody[16] observed, in some cases of cardiac disease, that a lowered tension of the alveolar carbon dioxide was present during the dyspneic period followed by a rise when compensation was regained.

The relation between the alveolar and arterial carbon dioxide tensions was studied by Peters and Barr[17] who found that the alveolar values were decidedly lower than the arterial in advanced decompensation. The same observation was noted by Campbell and Poulton[18].

The carbon dioxide dissociation curves of the blood were found by Peters and Barr[17] to be at normal levels in mild or moderate cardiac insufficiency but definitely reduced in certain cases of advanced heart failure, particularly those with marked cyanosis.

The H-ion concentration of the arterial blood in cardiac disease may be altered by associated pulmonary or renal disease, administration of morphine and other complicating factors. In general it has been reported to be within normal limits in mild or moderate degrees of heart failure and definitely acid in extreme failure, with return to normal when compensation was restored (Peters and Barr[17]). Instances of an alkaline pH in a few cases of cardiac dyspnea have been reported by Campbell and Poulton[19].

In 1908 Beddard and Pembrey[20] observed that the inhalation of oxygen resulted in a decreased pulmonary ventilation in a patient with cardiac insufficiency. This finding was later reported by Campbell, Hunt and Poulton[21] who observed also a corresponding increase in the carbon dioxide concentration of the expired air. It is interesting to note that in normal animals living in high oxygen atmospheres, J. A. Campbell[22] noted an increase in tissue tensions of both oxygen and carbon dioxide.

Recently, Baker[23] reported a case of bundle branch block in which inhalation of oxygen resulted in a disappearance of the aberrant ventricular complexes and a striking improvement in intraventricular conductivity.

Results

In this communication we wish to present the results of studies of the effects of oxygen therapy in various types of heart disease done in collaboration with D. W. Richards[24] and R. L. Levy[25] at the Presbyterian Hospital, New York, during the past three years. Since one of the handicaps in the previous studies of the therapeutic use of oxygen has been that it was generally administered ineffectively, we shall note briefly the methods of oxygen therapy which we employed. The Barach oxygen chamber[26] and oxygen tent[27] were employed to administer 40 to 50 per cent oxygen. In the oxygen chamber a constant temperature and humidity regulation was achieved and in the oxygen tent the temperature was kept below 70 degrees and the humidity below 50 per cent. In the treatment of patients with dyspnea it is of the greatest importance, not only to be accurate in the determination of the oxygen concentration employed but also to provide a comfortable atmospheric environment. Oxygen therapy will not be successful if types of apparatus are used which do not effectively remove the heat and moisture eliminated by the patient, in addition to furnishing 40 to 50 per

cent oxygen in the inspired air. In some cases when lower oxygen concentrations were employed, the nasal catheter was used to furnish 30 to 35 per cent oxygen as described in a previous article[28].

We wish to report upon the therapeutic use of oxygen in twenty patients who may be classified under the following four headings:

1. Congestive heart failure due to primary cardiac disease.

2. Cardiac insufficiency developing as a sequel to chronic pulmonary disease.

3. Acute coronary thrombosis.

4. Coronary arteriosclerosis with chronic cardiac pain.

1. Congestive Heart Failure Due to Primary Cardiac Disease*

The effects of living for two to five weeks in an atmosphere containing 45 per cent oxygen were studied in eight patients with congestive heart failure by Dr. Richards and myself. Although there was a considerable variation in their pathology, from a clinical standpoint they were all cases of advanced cardiac insufficiency. All were cyanotic, suffered from dyspnea at rest, and all except one had marked orthopnea and generalized edema. The patients were first observed from one to eight weeks on the ward on routine treatment. When there appeared to be no further clinical improvement or when the patient was definitely losing ground, transfer was made to the oxygen room where the patient inspired 45 per cent oxygen.

In four patients who suffered from degenerative heart disease characterized by intense dyspnea and orthopnea, marked cyanosis and peripheral edema, the major effects of residence in an atmosphere of 45 per cent oxygen were:

(1) Marked subjective improvement, decrease of cyanosis, relief of dyspnea, orthopnea and cough, beginning generally within three hours after their entrance into a high oxygen atmosphere.

(2) Increase of urinary output and disappearance of edema, of gradual onset and usually not reaching its maximum for three to five days. In three patients a return to normal atmospheric oxygen resulted in a decreased urinary output and a return of edema. Raising the oxygen concentration again brought about a second diuresis. In two, this sequence was obtained both by transferring the patient from the oxygen room to the ward, and by lowering and raising the oxygen within the chamber without removing the patient.

(3) Increased arterial oxygen saturation.

(4) Sharp rise in carbon dioxide content of arterial blood, and in carbon dioxide curve level, in high oxygen.

(5) Decreased pulmonary ventilation.

(6) Lowered pulse rate.

(7) In the case of one patient other measurements showed: (a) slight increase in cardiac output, (b) sharp fall in blood lactic acid from 22.6 mg. to a normal value of 7 mg.

*Complete data in paper by Barach, A. L., and Richards, D. W., Effects of treatment with oxygen in cardiac failure, Arch. Int. Med., 1931, xlviii, 325.

In these cases, all of whom may be said to have improved in 45 per cent oxygen, there were other changes which occurred, although not constantly: lowered respiratory rate, lowered body temperature, decreased basal metabolism, slightly higher arterial pH, increase in vital capacity and fall in red blood count and hemoglobin.

Two other cases had advanced and active rheumatic heart disease, with cyanosis, generalized passive congestion, edema, and irregular fever. Subjectively, they were more comfortable and less dyspneic in high oxygen; their cyanosis was somewhat improved and comparative measurements on one case showed an increase in arterial oxygen saturation from 84 to 93 per cent. There was in each case a moderate rise in carbon dioxide curve level. Little change, however, occurred in the edema, and there was no tendency to diuresis. However, one patient was removed rather abruptly from 45 per cent oxygen to the ward, where she rapidly went into collapse, with renal suppression for 20 hours, low blood pressure, and profound cyanosis. Her arterial oxygen saturation again went down to 84 per cent (this measurement was taken when patient was receiving four liters of oxygen per minute by nasal catheter), carbon dioxide dropped to the remarkably low value of 26.4 volumes per cent, and arterial pH fell from 7.44 to 7.30. After return to 45 per cent in the chamber, she recovered quickly to her former state. During the next 24 hours she passed 1000 c.c. of urine. These two patients both showed lowered pulse rate while in high oxygen.

Finally, two patients showed practically no reaction whatever to the increase in atmospheric oxygen. One was a man of 54, with long-standing mitral stenosis, great cardiac enlargement, enlargement of the liver, but no edema and no orthopnea. Clinically, he was moderately cyanotic, but this was evidently of venous origin as his arterial blood when he was in the ward was 91 per cent saturated with oxygen or better. The development of a mild rhinitis and bronchitis with a transient lowering of the carbon dioxide curve, and of the vital capacity, seemed to be the only change while he was in the oxygen room. Subjectively, he was no better.

The second was a girl of 13 with congenital heart disease, later shown by autopsy to be the tetralogy of Fallot, combined with a patent ductus arteriosus. The case is being reported by Dr. Richards[29] in further detail elsewhere. It is sufficient to note here that her arterial oxygen saturation, about 60 per cent, was increased only slightly, to 65 per cent, in high oxygen, that there was no change in her carbon dioxide or in her urinary output, that her pulmonary blood flow was practically unaltered, and that subjectively she was not improved. She did not have any edema at any time. She was not in the oxygen room long enough to rule out the possibility of a change in urinary output relative to intake.

II. Cardiac Insufficiency Developing as a Sequel to Chronic Pulmonary Disease

The effects of oxygen therapy were studied in five cases of cardiac insufficiency due to previous chronic

pulmonary disease: two cases of pulmonary tuberculosis, two cases of fibrosis of the lung and one case of emphysema. In these patients, treatment with oxygen was carried on during a period of two to seven months. The tuberculous patients had active tuberculosis with extensive pathology in their lungs. They were both dyspneic at rest, cyanotic, with an elevated temperature and pulse rate. In each instance, residence in the oxygen chamber was followed by increase in comfort, lessened dyspnea, and other evidences of clinical improvement such as increased appetite and lowered pulse rate. In one of them the symptoms of respiratory failure were extreme, and the inhalation of 45 per cent oxygen appeared to prolong life until the acute processes had somewhat subsided. No effect, however, was noted on the progress of the tuberculous lesion itself. In one who had been in the oxygen chamber for two and one-half months a marked rise in arterial carbon dioxide was associated with the increase in the arterial oxygen saturation.

The first patient with fibrosis of the lung was a woman of forty-nine years of age who suffered from progressively extreme dyspnea, marked cyanosis, and paroxysmal coughing for two years. Her respirations were 60 per minute, very shallow, pulse rate 110 without fever. She was kept in an oxygen chamber for six months. During the first month her respirations declined to as low as 28 per minute, pulse to 80 with relief of dyspnea and complete disappearance of coughing. The fibrosis of the lung, however, steadily advanced and it became necessary to give her increasing concentrations of oxygen, from 40 per cent at the start to 55 per cent at the termination of her illness. She died as a result of cerebral thrombosis. A week before her death the arterial oxygen saturation was 89 per cent and the arterial carbon dioxide content had reached the extraordinary figure of 132.1 volumes per cent. (In the cases of congestive heart failure relieved in high oxygen, the arterial carbon dioxide content was elevated from a range of 35 to 40 volumes per cent before oxygen treatment to 45 to 70 volumes per cent after oxygen treatment.) In the second case of fibrosis of the lung which was associated with marked cardiac insufficiency the arterial carbon dioxide content rose from 35.4 volumes per cent to 69.9 volumes per cent and subsequently as improvement in pulmonary function occurred dropped to 48.9 volumes per cent. This patient for a period of five months appeared unable to live without oxygen. Whenever oxygen was discontinued he became dyspneic, cyanotic, and began to accumulate edema fluid. However, at the end of five months oxygen therapy was stopped without recurrence of symptoms of cardiac or respiratory failure. For eight months he was able to go about on restricted activity without distress. At the end of this time slight symptoms of cardiac failure became evident and the patient was put on nasal oxygen for a varying number of hours (2 to 4) during the day.

The patient with emphysema was a man of fifty who suffered from progressive impairment of pulmonary function for a period of seven years. At the time he was seen cardiac insufficiency was so marked as to presage a fatal outcome. He was intensely

cyanotic and dyspneic, gasping at every breath, with a rapid pulse of poor quality. He was treated in an oxygen tent with 50 per cent oxygen for ten days with disappearance of dyspnea and cyanosis. His pulse gradually improved in volume and dropped from 100 to 76. After continuous nasal oxygen at 4.0 liters a minute through a catheter for one month, nasal catheter treatment was continued for six to eight hours daily, for the following three months. After this period he was able to resume ambulatory activity without oxygen.

III. Acute Coronary Thrombosis

Dr. Levy and I studied the effects of the administration of 45 per cent oxygen by means of the oxygen tent in four patients suffering from coronary thrombosis. All were critically ill. The following observations were made in these cases:

1. Subjective improvement occurred in from one to three hours after the administration of oxygen was begun. This manifested itself chiefly by relief of respiratory embarrassment and restlessness.

2. Cyanosis was diminished or abolished.

3. The respiratory rate was slowed and Cheyne-Stokes breathing, if present, tended to disappear.

4. The heart rate became slower. The heart sounds grew stronger and the volume of the pulse improved.

5. Removal of the oxygen tent before satisfactory readjustment of circulatory conditions had taken place resulted in a recurrence of the symptoms and signs just enumerated.

In sudden thrombotic closure of a branch of the coronary artery there results an abrupt interference with the blood supply of the heart which induces an initial state of shock. The degree of functional disturbance that follows depends on the caliber and location of the occluded vessel, as well as on the distribution and anastomoses of the coronary system in the affected individual. If the resulting area of myocardial infarction is large, signs and symptoms of congestive heart failure may ensue. The cardiac action becomes weak, rapid and often irregular. The blood pressure falls sharply and remains at a relatively low level. Cyanosis appears, and moist râles are heard at the bases of the lungs. Respiration is accelerated and difficult. The picture is one of acute oxygen-want due to myocardial insufficiency.

Employment of oxygen therapy (preferably in a concentration of from 45 to 50 per cent) may aid in maintaining an adequate circulation until the heart has had an opportunity to recover from its acute functional disturbance. Obviously, the cardiac injury may be so severe that recovery is impossible. But in some instances effective use of oxygen may be responsible for the saving of life.

The responses of the cases studied allow the conviction that anoxemia and its treatment may play a crucial rôle in determining the outcome after coronary thrombosis.

IV. Coronary Arteriosclerosis with Chronic Cardiac Pain

I have recently studied three cases of coronary arteriosclerosis with chronic cardiac pain in men in the fifth

and sixth decades of life. All these patients had one to five attacks of cardiac pain daily at rest in bed before treatment with oxygen. They were treated by residence in the oxygen chamber with 50 per cent oxygen for a period of two weeks. In the first, which was the most severe, the attacks gradually decreased in number and severity, but promptly recurred when the patient was removed from the chamber. His condition was at all times exceedingly grave and he died three weeks after removal from the oxygen chamber. In the second case the attacks of pain gradually disappeared. After removal from the oxygen room the pains recurred to a slight extent but permitted the patient to return home. During the following six months he has been markedly improved over his previous condition, having only a comparatively small number of attacks of mild pain, i.e., two to three attacks a month, none of them requiring more than rest and nitroglycerin.

The third patient was less severely affected than the others, averaging one attack of pain daily at rest in bed in the hospital before admission to the chamber. During ten days residence in 45 per cent oxygen he had one attack of pain, and felt extremely well. For six weeks after he was able to resume restricted activity without pain. At that time, however, pain recurred, waking him up during the night. He was placed on nasal oxygen, 4.0 liters per minute for eight hours a day for six weeks and since that time, a period of four months, he has had only occasionally mild pain on activity and is not awakened at night by cardiac pain.

Discussion

The improvement which was evident in the cases of acute coronary thrombosis after inhalation of 45 to 50 per cent oxygen indicates the importance of the factor of oxygen-want in this condition. After coronary closure there is first a pronounced anoxemia of the heart muscle, followed by anoxemia in the venous blood as a result of the impaired heart action and, very soon after, an arterial anoxemia due to the development of passive congestion and edema of the lungs. The inhalation of 45 to 50 per cent oxygen tends to remove the arterial anoxemia and prolong life until the heart is able to compensate, if it is possible to do so, for its acute disturbance in function. The prompt collapse which follows withdrawal of oxygen before the heart muscle has adapted itself to the closure makes manifest the significance of arterial anoxemia in the symptomatology of the disease.

The problem of interpreting the origin of cardiac pain is complicated by the fact that no afferent nerve fibres are to be found in the heart muscle or its blood vessels. The possibility is present that supposedly efferent sympathetic nerves in the heart muscle may carry afferent impulses. Wiggers[31] observes in a recent review that although "Sir Clifford Allbutt maintained to the end of his life that cardiac angina could arise only from stimulation of the nerve fibres terminating in the outer coats of the aorta, a great deal of clinical and even a little experimental evidence exists that anoxemia of the heart muscle—regardless of whether it is produced by cor-

onary embolism, thrombosis or sclerosis. . .—is capable of inaugurating serious attacks of cardiac pain." That local anoxemia of the heart muscle may produce pain is certainly suggested by the relief of pain in the three cases of coronary arteriosclerosis who were treated in the oxygen room.

Although we cannot entirely explain the mechanism by which relief of pain occurs in cases of coronary arteriosclerosis without cyanosis or evident anoxemia, we have obtained some knowledge that bears on the problem. In the first place, the inhalation of 50 per cent oxygen in normal men we have found capable of raising the arterial oxygen saturation from 95 to 99 per cent. In one of the cases of coronary arteriosclerosis which we measured, the arterial oxygen saturation was raised from 94 to 99 per cent. Although this represents a small increase in per cent saturation, it indicates a very considerable rise in the tension or partial pressure of oxygen available to the tissues (because of the shape of the oxygen dissociation curve), and provides therefore a possible explanation for relief of local anoxemia in the heart muscle. The inhalation of high concentrations of oxygen causes the normal heart to beat at a slower rate,[30] and affects more markedly the heart in cardiac insufficiency,[12,24] which suggests a lessened strain due to a greater oxygen supply.

The most interesting and striking effects of oxygen therapy in the cases of cardiac insufficiency, both those due to local disease of the heart itself and those in which heart failure appeared to be secondary to primary pulmonary disease are: (1) Relief of dyspnea and orthopnea, (2) elevation of the arterial carbon dioxide content and of the level of the carbon dioxide dissociation curves, and (3) diuresis.

1. The relief of dyspnea which frequently manifests itself within several hours after removal to an oxygen-enriched atmosphere indicates that oxygen-want plays a decisive rôle in the production of cardiac dyspnea. We may briefly review at this point some of the known factors involved in the production of shortness of breath in cardiac insufficiency.

Passive congestion and edema in the lungs was noted by von Basch[32] as resulting in a stiffening of the lung with consequent impairment of the expansile capacity of the lungs, or vital capacity. Siebeck[33] also found that the lung expands unequally in cardiac insufficiency and thus makes for an imperfect mixture of the gases in the lung, with resultant impairment of normal diffusion of oxygen. In addition to these difficulties in moving the lung, there must also be a decreased diffusion capacity of the swollen alveolar membrane for respired gases, especially oxygen. The end result of pulmonary dysfunction is insufficient oxygen saturation of the arterial blood. This involves all the tissues in the consequences of anoxemia, many of which have been noted in the introduction. An additional one may be commented upon at this point, namely, lactic acid accumulation (Araki[34]), (MacLeod[35]). An accumulation of lactic acid is of particular interest with reference to the respiratory center. At the present time the most satisfactory explanation of the respiratory stimulus

is that it is governed by the acidity of the tissue of the respiratory center (Douglas and Haldane[36]), (Winterstein[37]), (Gesell[38]).

When in our cases the clearing of arterial anoxemia resulted from the inhalation of 45 to 50 per cent oxygen, dyspnea was relieved and gradually disappeared. It is evident (1) that the difficulties in oxygen absorption resulting from lung stiffening, decreased vital capacity and swollen alveolar membranes were overcome, and (2) that the increased oxygen saturation of the pulmonary blood tends to diminish tissue acid accumulation. In the one case measured, the blood lactic acid rapidly returned to normal following the inhalation of oxygen. That the respiratory stimulus was thereby decreased is evidenced by the lowered pulmonary ventilation and that there was some diminution in general tissue acidity was suggested by the small but constant lowering of arterial H-ion concentration which we observed.

The difficulty of eliminating carbon dioxide has also been stressed as an important factor in the causation of cardiac dyspnea, which brings us to the second result of oxygen therapy to be discussed.

2. The marked rise in carbon dioxide content of the arterial blood was constantly associated with (1) clinical improvement, (2) increased arterial oxygen saturation, and (3) impairment of pulmonary function in respect to the absorption of oxygen.

If the inhalation of oxygen-enriched air makes possible a lower pulmonary ventilation it is obvious that an increase in blood carbon dioxide levels and hence in alveolar air will permit the elimination of a greater amount of carbon dioxide with a lower pulmonary ventilation. In the cases of congestive failure due to primary cardiac disease the arterial carbon dioxide content was elevated from a range of 35 to 40 volumes per cent to 45 to 70 volumes per cent, after oxygen treatment. This increase in the carbon dioxide levels in the blood did not, however, represent a carbon dioxide acidosis due to deficient elimination of carbon dioxide, since the H-ion concentration of the blood was never more acid but on the contrary, tended to be slightly less acid when the carbon dioxide became elevated. It is therefore evident that carbon dioxide diffuses through the lungs in higher concentrations when anoxemia and its consequences are relieved. This fact necessitates an alteration in the conception of previous investigators concerning the rôle of carbon dioxide in the causation of cardiac dyspnea.

Wiggers[31] remarks in a recent review of the physiology of cardiac dyspnea that "Neither an excess of carbon dioxide, as in exercise, nor the existence of a fixed acidosis is separately responsible for the dyspnea. But a moderate grade of fixed acidosis combined with pulmonary congestion which prevents the compensatory elimination of carbon dioxide might easily produce augmented breathing in heart disease. . . . In the light of this conception, also, it appears to be a basic fact that impairment of the pulmonary circulation is the ultimate cause that prevents the free compensatory elimination of carbon dioxide."

Our studies, however, indicate that lack of oxygen plays the primary rôle in the production of cardiac dyspnea. Passive congestion of the alveolar membranes of the lung and the associated decreased vital capacity impair, first of all, the diffusion of oxygen into the pulmonary veins, resulting in arterial anoxemia and the consequences of oxygen-want in the tissues, such as accumulation of lactic acid. When the anoxemia is relieved, there is a constant and marked rise in the carbon dioxide concentration of the blood with an *even greater elimination* of carbon dioxide per breath through the congested lung. Thus, in one of the cases of congestive failure, the carbon dioxide content of the arterial blood rose from 38.4 to 69.9 volumes per cent in four days. It appears, therefore, likely that the elevation in carbon dioxide level in the blood is an adaptive change which is readily accomplished if sufficient oxygen is supplied to maintain normal metabolic activity. Also, lactic acid accumulation disappears when anoxemia is relieved. It seems probable that base to retain carbon dioxide is in part derived from the blood lactates in this manner. A decrease in pulmonary ventilation follows with a lessened sense of pulmonary effort and therefore relief of dyspnea.

To summarize, then, cardiac dyspnea was relieved (1) by the provision of an adequate oxygen supply to the tissues, (2) by the development of a mechanism of eliminating carbon dioxide by increasing the concentration in the blood, and (3) by the oxidation of an excessive accumulation of lactic acid in the blood.

We may consider now the general factor involved in the increase in blood carbon dioxide which follows oxygen treatment in the cases of cardiac failure as well as in the cases of chronic pulmonary disease. This appears to be the extent of impairment of pulmonary function in respect to the absorption of oxygen. In the patient with fibrosis of the lung in whom a progressive impairment of the function of the lung took place so that 55 per cent oxygen became necessary to support life, the blood carbon dioxide reached 132.1 volumes per cent. It would appear that this extraordinary high concentration of carbon dioxide in the alveolar air represented a mechanism capable of eliminating carbon dioxide in the presence of an extreme diminution of lung function. In the second patient with fibrosis of the lung and cardiac insufficiency, the carbon dioxide in the arterial blood rose from 38.4 to 69.9 after four days' oxygen treatment, and then, as the patient improved, dropped to 48.9 volume per cent, even though he was still breathing an oxygen-enriched atmosphere. Thus, when the function of the lung, if severely impaired, was relieved by the inhalation of oxygen, the carbon dioxide concentration in the blood and in the alveolar air became elevated, as an adaptive reaction noted above. But when the pulmonary function improved in respect to the absorption of oxygen, the carbon dioxide concentration in the blood and alveolar air diminished.

Although the carbon dioxide in the blood declines after clinical improvement has taken place whether the patient is breathing oxygen or air, a slight increase in blood carbon dioxide

may still persist in a high oxygen atmosphere. It has been noted in animals kept in oxygen-enriched atmospheres that an increase in carbon dioxide tension in the tissues occurs (Campbell[22]). The significance of the elevation in carbon dioxide in normal animals exposed to high oxygen is not clear. As far as our purposes are concerned, the rise in carbon dioxide following oxygen treatment in patients suffering from dyspnea appears to be an adaptive mechanism for eliminating carbon dioxide, accompanied by a decreased pulmonary ventilation which is made possible only by the relief of anoxemia and its consequences.

3. The diuresis and disappearance of edema was a marked feature of four of our cases. The physiologic explanation of cardiac edema is itself by no means clear, but three factors have been described: (1) edema of the dependent parts due to stasis and physical filtration, (2) impairment of renal function due to congested glomerular membranes, and (3) altered permeability of capillaries due to anoxemia[41]. Oxygen therapy resulted in an improved state of the circulation which would tend to remove the edema due to stasis as well as relieve the passively congested glomerular membranes. In so far as the tissue cells of the body are altered in their permeability due to anoxemia, an increased supply of oxygen would likewise be beneficial. Other alterations in tissue water balance may also be implicated concerning which our data give no information.

I am conscious that this discussion of the therapeutic use of oxygen in heart disease displays many large gaps in our knowledge. It is our hope, however, that these observations will stimulate further studies in which effective and comfortable methods of administering oxygen will fulfil the prophecy of Priestley shortly after he had discovered oxygen 157 years ago:

"My reader will not wonder", says Priestley,[42] "that, after having ascertained the superior goodness of dephlogisticated air (that is, oxygen), by mice living in it and by the other tests above mentioned, I should have the curiosity to taste it myself. I have gratified that curiosity by breathing it, drawing it through a glass syphon, and by this means I reduced a large jar full of it to the standard of common air. The feeling of it to my lungs was not different from common air, but I fancied that my breath felt peculiarly light and easy for some time to come. Who can tell but that in time this pure air may become a fashionable article in luxury? Hitherto only two mice and myself have had the privilege of breathing it."

Summary

The therapeutic use of oxygen was studied in eight patients with congestive heart failure due to primary cardiac disease, in five cases of cardiac insufficiency developing as a sequel to chronic pulmonary diseases, in four cases of acute coronary thrombosis and in three cases of coronary arteriosclerosis with chronic cardiac pain.

In the cases of congestive heart failure the most striking effects observed were (1) relief of dyspnea and orthopnea, (2) diuresis and disappearance of edema, and (3) a marked rise in the carbon dioxide content of the arterial blood. Other observations noted were relief of cyanosis, in-

creased arterial oxygen saturation, decreased pulmonary ventilation, lowered pulse rate and decrease in blood lactic acid.

In the cases of acute coronary thrombosis life appeared to be prolonged by the inhalation of an oxygen-enriched atmosphere until the heart was able to recover from its acute functional disturbance. The cases of coronary arteriosclerosis with chronic cardiac pain were relieved by residence in a high oxygen atmosphere.

These results indicate that oxygen-want plays the primary rôle in the production of many forms of cardiac dyspnea. The increase in carbon dioxide content of the arterial blood occurs as an adaptative change which facilitates the elimination of carbon dioxide.

The clinical improvement which patients suffering from the various forms of heart failure experience suggests a new employment of oxygen therapy by effective methods in these conditions.

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The Reaction to Nitrites in the Anginal Syndrome and Arterial Hypertension*

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SINCE the introduction of the use of amyl nitrite by Sir Lauder Brunton in 1867 nothing has been found to excel the nitrites for the relief of the pain in angina pectoris. Although the pharmacology of the members of this group has been exhaustively studied the question as to the mode of their action in anginal pain has never been definitely settled. This is due partly to the fact that the cause of the pain has not been thoroughly understood. Furthermore, because of their known action on the walls of the peripheral arterioles resulting in a lowering of blood pressure, the nitrites have been used in attempts to cause either temporary or permanent lowering of the pressure in patients suffering from arterial hypertension and are therefore of interest to the clinician. The relaxability of the walls of the arterioles as measured by the drop in diastolic pressure after the inhalation of amyl nitrite has also been studied in an attempt to estimate the prognosis in these cases[1]. It has seemed worth while, therefore, to make a series of simple clinical tests by means of repeated blood pressure estimations of the reaction which the rapidly acting drugs, amyl nitrite and nitroglycerine produce in three types of people—the normal, those with arterial hypertension and those who are suffering from attacks of the so-called "ambulatory" angina pectoris.

No attempt will be made to enter into an exhaustive discussion of the pharmacology of the nitrite group. The familiar text book description mentions the flushing of the face, headache, and tachycardia after the inhalation of amyl nitrite, and the rapid fall in blood pressure due to a direct action on the smooth muscle cells of the walls of the arterioles and veins. A similar but less rapid effect is attributed to nitroglycerine. Anyone who has tested the amyl nitrite on himself can bear witness to the very unpleasant nature of the subjective symptoms produced in a normal person. That the tachycardia is due to vagus action has been shown, as it does not occur in experimental animals if the nerve has been severed. It has been amply demonstrated that the fall in pressure is due to a direct action on the vessel walls.

The statement is common that in hypertension generally the action of amyl nitrite and nitroglycerine is to

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produce a sharp and temporary fall in blood pressure[2] although no detailed studies of this action on systolic and diastolic pressure are available. Stieglitz[3] has recently emphasized the importance of a fall in diastolic pressure in these cases after the inhalation of amyl nitrite as indicating that the peripheral arterioles have not yet reached an advanced state of sclerosis and therefore that the prognosis may still be favorable. He recommends that the pressure be taken at the height of the symptoms; flushing, tachycardia, etc., and that the proportion of the distance that the diastolic has fallen toward 90 mm. be taken as the indication of arteriolar relaxability.

The action of the nitrites on the cerebral circulation is of especial interest to those who have attempted to relieve headache in cases of arterial hypertension by their use. It has been clearly shown[4] that the pial vessels are dilated by these drugs and that intracranial pressure is increased[5]. The writer has seen a severe headache in a patient with marked arterial hypertension made almost intolerable by a dose of 1/100 grain of nitroglycerine which, by the way, had no appreciable effect on the blood pressure (see Chart 4).

The effect of the nitrites on the pulmonary circulation is apparently the opposite of that on the general circulation. Isolated strips of pulmonary artery have been noted to contract when in contact with the nitrites[6] and a rise in pulmonary pressure has been demonstrated after their use.

As regards the coronary arteries the statement is made that they also are dilated as are other peripheral arteries. Dilation of isolated rings of coronary artery[7] and increased outflow from the coronary veins have been shown to be the result of nitrite action by some observers,[8] while others have been unable to produce experimentally, any definite evidence of such action[9]. Perhaps, however, the best demonstration of the effect on the coronaries is that by Smith[10] who showed in dogs' hearts in which artificial infarction had been produced by ligation of the coronary branches an actual decrease in the cyanosis of the infarcted areas due to increased collateral circulation following the intraventricular injection of 1/200 grain of nitroglycerine.

The demonstration of an increase in coronary flow by the nitrites is of great importance in upholding the view that the pain in angina pectoris is caused by ischemia of the heart muscle, so ably championed by Keefer and Resnik[11]. These investigators are, however, very sceptical as to the likelihood of "coronary spasm" as a usual origin of the pain. Whatever may be the cause of the ischemia, it is safe to say that if this ischemia is the cause of the pain, dilation of the coronary arteries seems a reasonable mechanism of its relief. If, on the other hand, a tendency to stasis in the first part of aorta and in the coronaries is the cause of the pain, as believed by May[12], then, as he says, the dropping of the diastolic pressure by the nitrites is a reasonable mechanism for its relief. The following studies do, it is believed, throw some light on this question.

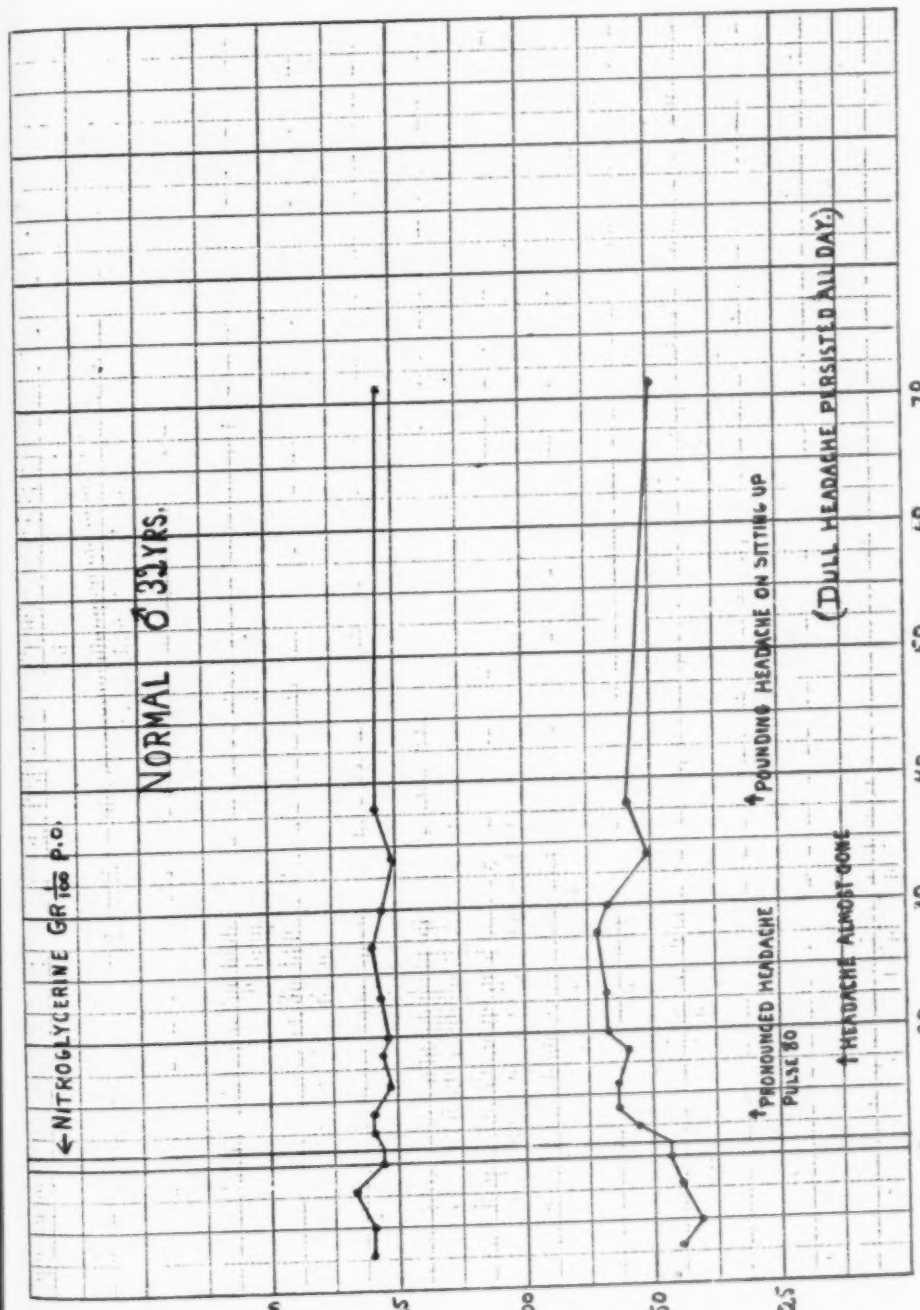

CHART 1. Normal reaction to nitroglycerine, gr. 1/100 by mouth.

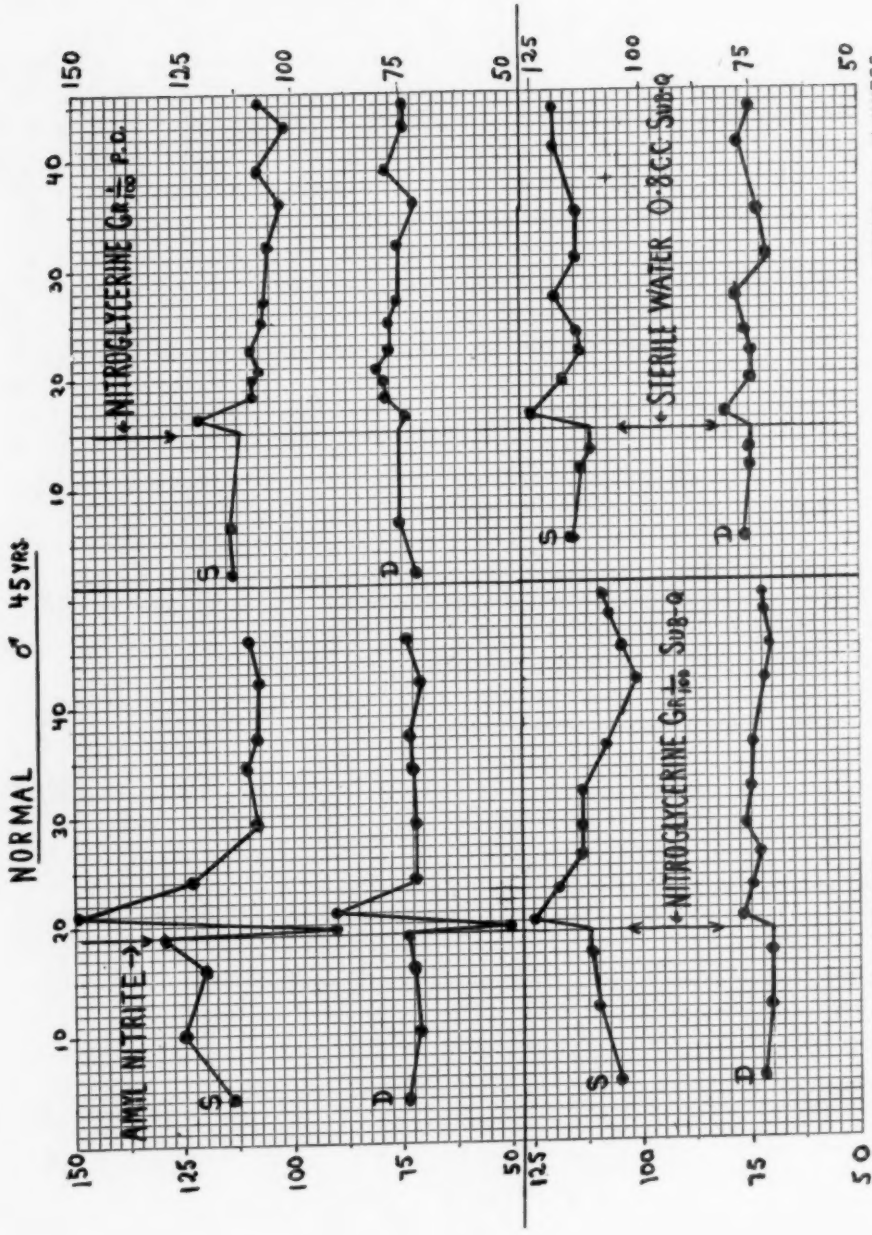

CHART 2. Normal reaction to nitroglycerine and amyl nitrite.

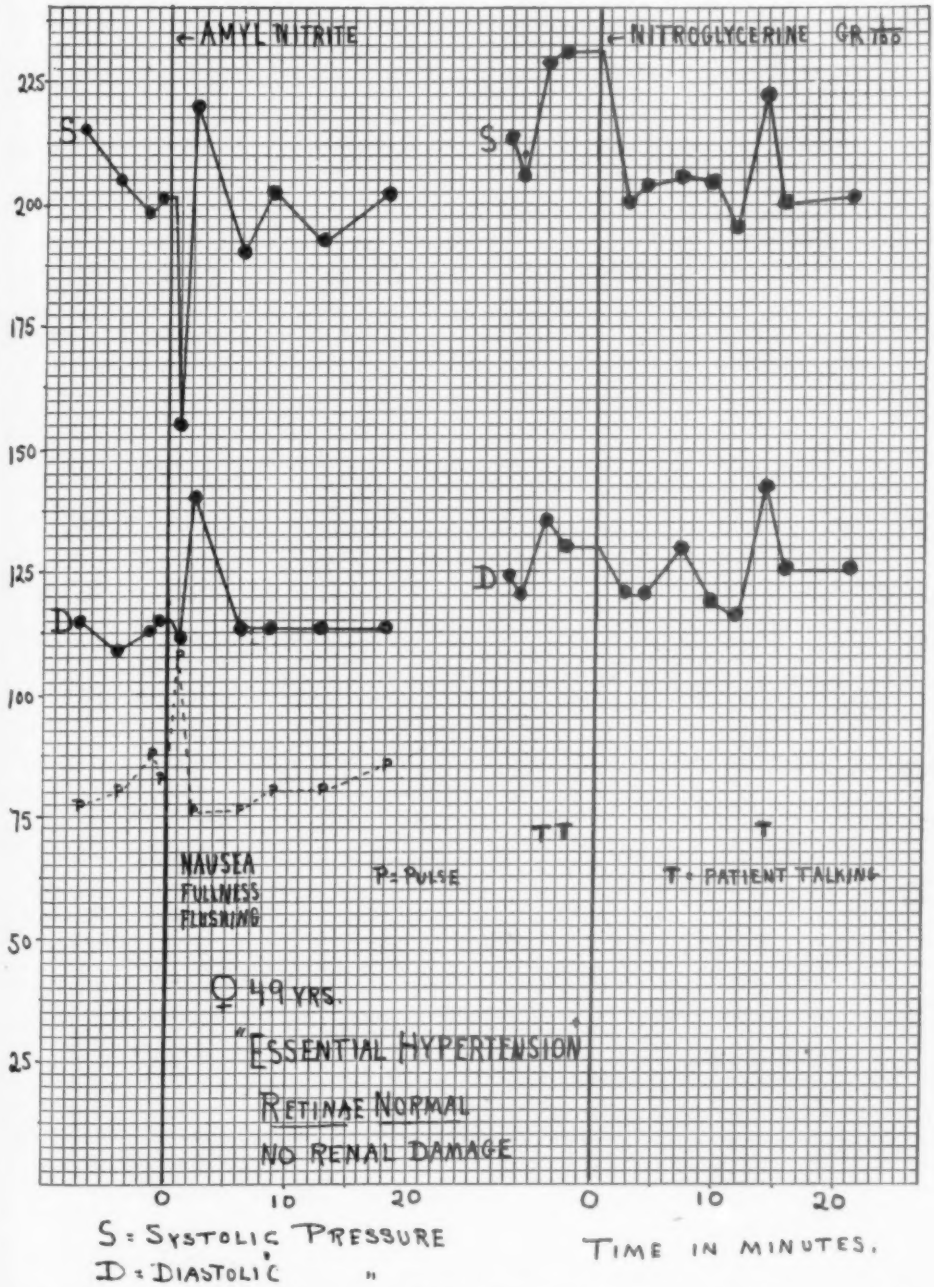

CHART 3. Arterial hypertension. Note absence of fall in diastolic pressure after amyl nitrite in spite of normal retinal vessels and kidneys.

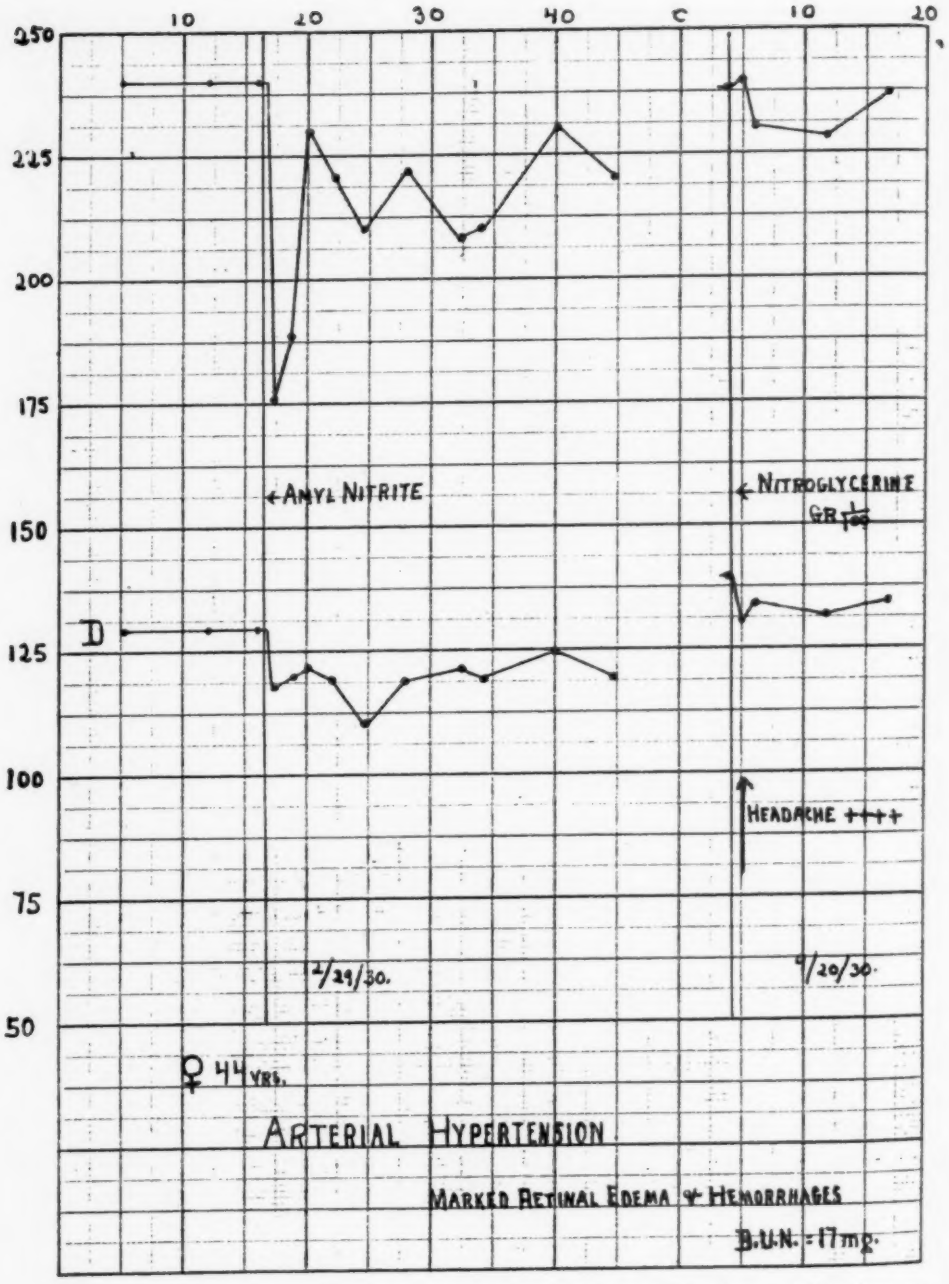

Chart 4. Arterial hypertension, severe, with marked retinal edema. Note increase in headache following nitroglycerine without fall in blood pressure.

The Reaction in the Normal Human Being

A few preliminary tests were made on normal persons. As Charts 1 and 2 demonstrate, the action was found to be as follows: (1) After nitroglycerine (either 1/100 or 1/50 grain dissolved in the mouth or gr. 1/100 subcutaneously) no immediate fall in blood pressure was noticed although there was a general tendency for the systolic pressure to fall during the next few minutes. Such a general decrease is also often noted in normal people with rest alone. No fall in diastolic pressure was noted. (2) After amyl nitrite an abrupt fall occurred in 30 seconds in both systolic and diastolic pressure. This was followed by a quick compensatory rise in both systolic and diastolic pressure sometimes to points above the original readings. After two minutes the pressure was not much different from that observed at the start and no further effect was noted except in some instances a slight tendency downward on the part of the systolic pressure. (See Chart 2.)

The Reaction in Arterial Hypertension

(1) Following the administration of nitroglycerine gr. 1/100 or 1/50 by mouth the majority of the sixteen patients studied by this method showed no constant effect on either systolic or diastolic pressure although a fall occurred in some instances. As a comparable fall is often noted[13] with rest alone it is probable that in these patients the lowering of pressure was due to the rest rather than to the drug. (Charts 3, 4, 5 and 9.) (2) After amyl nitrite in the twelve patients investigated, the same sudden drop was seen in systolic pressure as was noted in normals, but the subsequent rise did not as a rule reach the original height. The diastolic pressure fell markedly in some and not at all in others. It is worth noting that the fall in pressure after amyl nitrite is so rapid (occurring in 15 to 30 seconds) and that the compensatory rise occurs so quickly (1 to 2 minutes) that it is never possible to be sure that one has found the low point and in many instances this must have been missed. With regard to subjective symptoms it was found that these varied greatly in their severity and that neither their severity nor the time of their occurrence had any relation to the presence or absence of the fall in systolic or diastolic pressure. Furthermore, the presence or absence of a marked blood pressure fall could not be shown to have any definite relation to retinal arteriosclerosis or evidence of renal damage, as the charts demonstrate. Charts 3, 4, 6, 7, 8 and 9.)

The Reaction in Angina Pectoris

Before reporting the results of the reactions noted after the use of nitrites in attacks of so called "ambulatory" angina pectoris, it is perhaps worth noting that in every one of the eight patients studied the pressure during the attack and before treatment was instituted was found to be well above the usual pressures noted in these persons when they were free from attacks. This is contrary to the experience of Harlow Brooks

in these cases[14] but in accord with the writer's previous experience.

(1) The action of nitroglycerine was studied in fifteen attacks occurring in eight patients following 1/200 to 1/50 gr. by mouth. No change or a slight rise in systolic pressure occurred within the first minute. Usually within three minutes a marked drop in systolic and a slight drop in diastolic pressure took place. The maximum drop in systolic and diastolic pressure usually occurred within ten minutes. (Charts 10, 11, 12, 14, 15 and 16.)

Relief in Pain. Partial relief of pain ordinarily was noted in from one to two minutes, and complete relief except for residual soreness at times occurred within a minute and a half, and if the dose had been sufficient to control the situation had usually been established before the end of five minutes. It was evident that considerable or occasionally complete relief of pain took place in some cases before

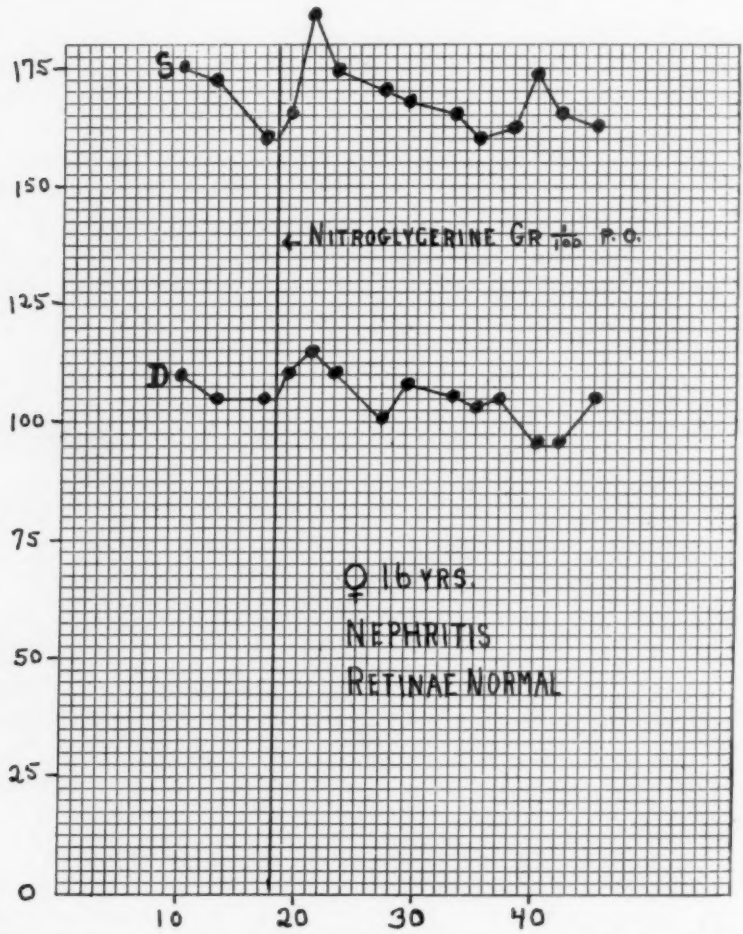

CHART 5. Nephritis with hypertension in a 16 year old girl. Note lack of response to nitroglycerine.

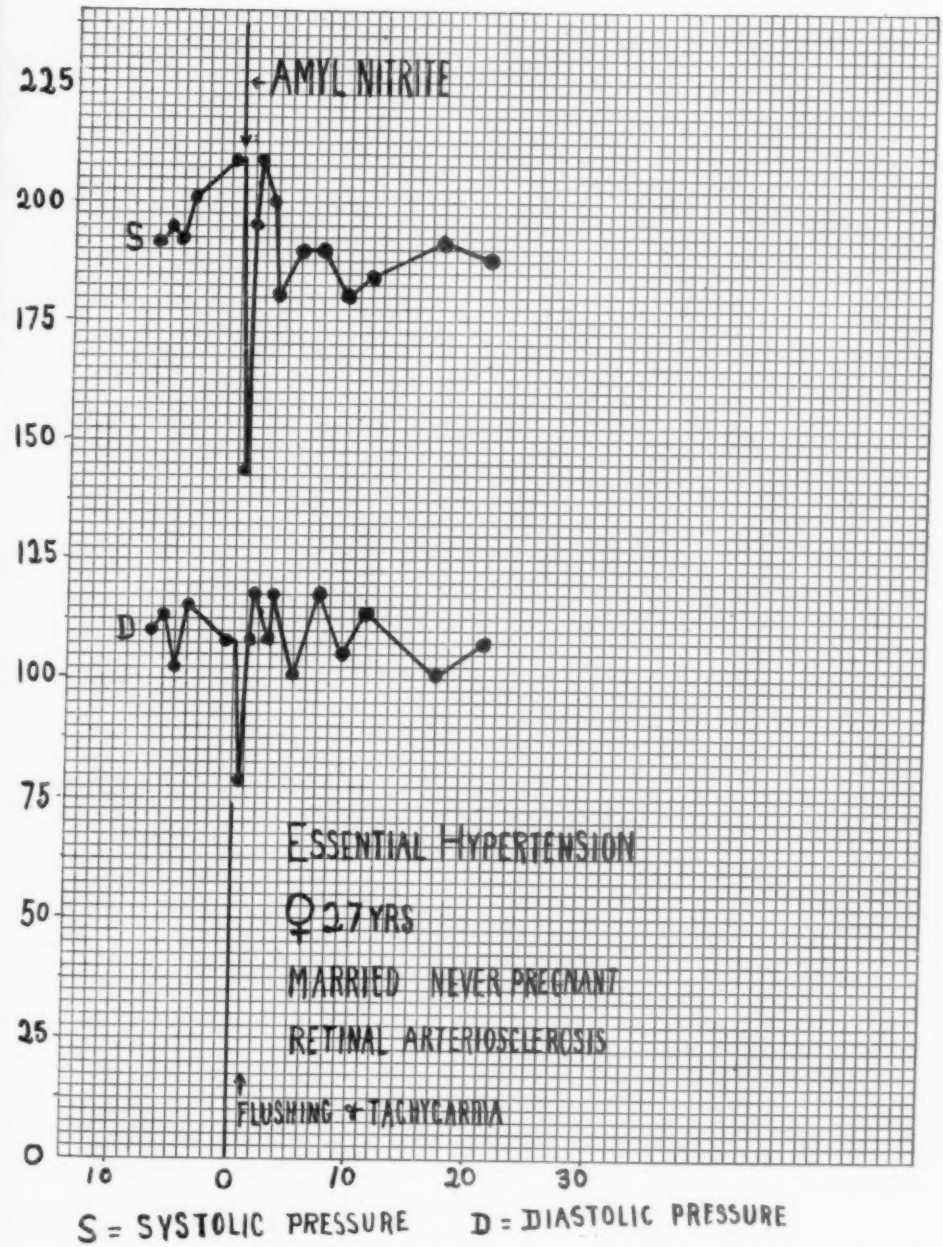

CHART 6. Arterial hypertension. Note marked fall in pressure after amyl nitrite in spite of evidence of retinal arteriosclerosis.

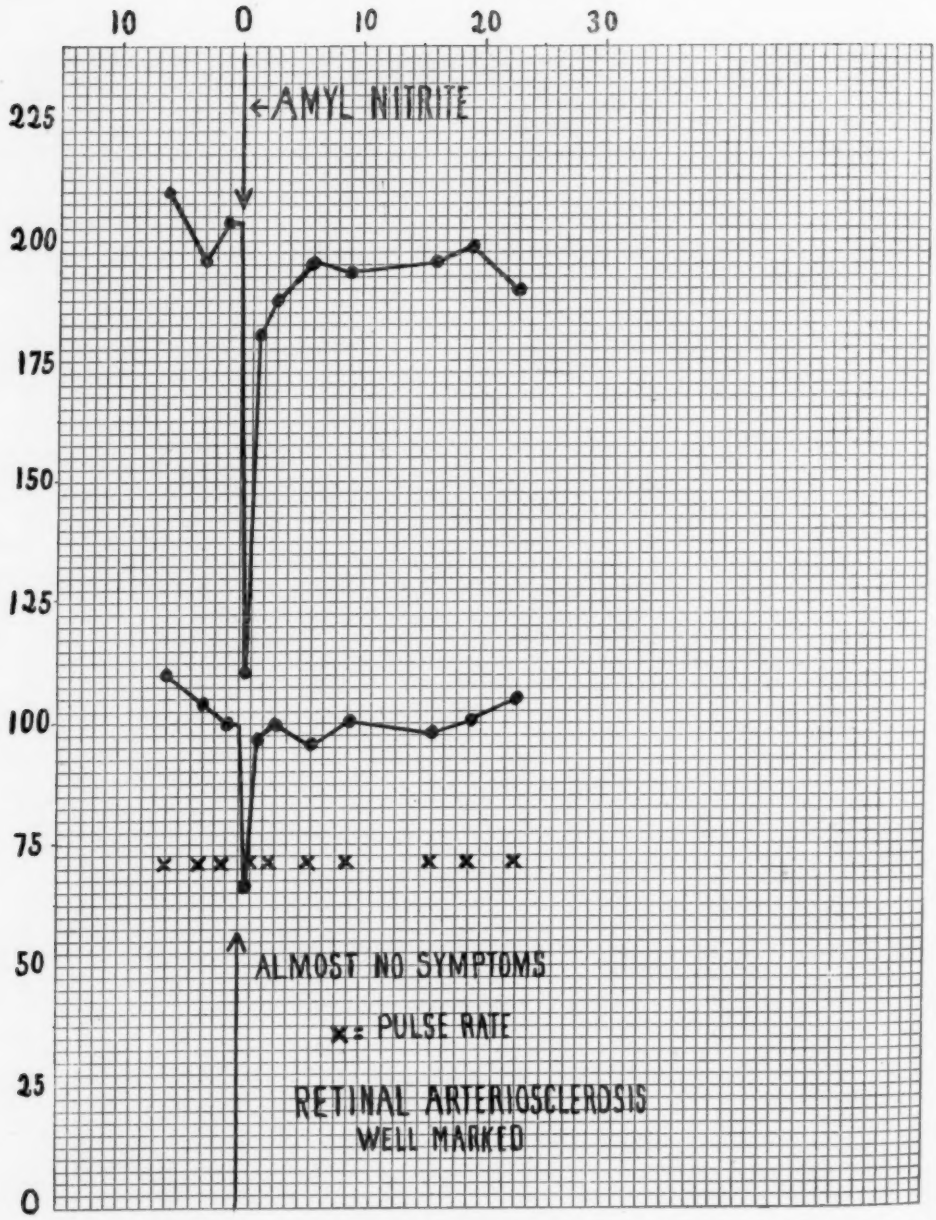

CHART 7. Arterial hypertension. Note marked response to amyl nitrite in spite of absence of tachycardia and other symptoms and in the presence of marked retinal arteriosclerosis.

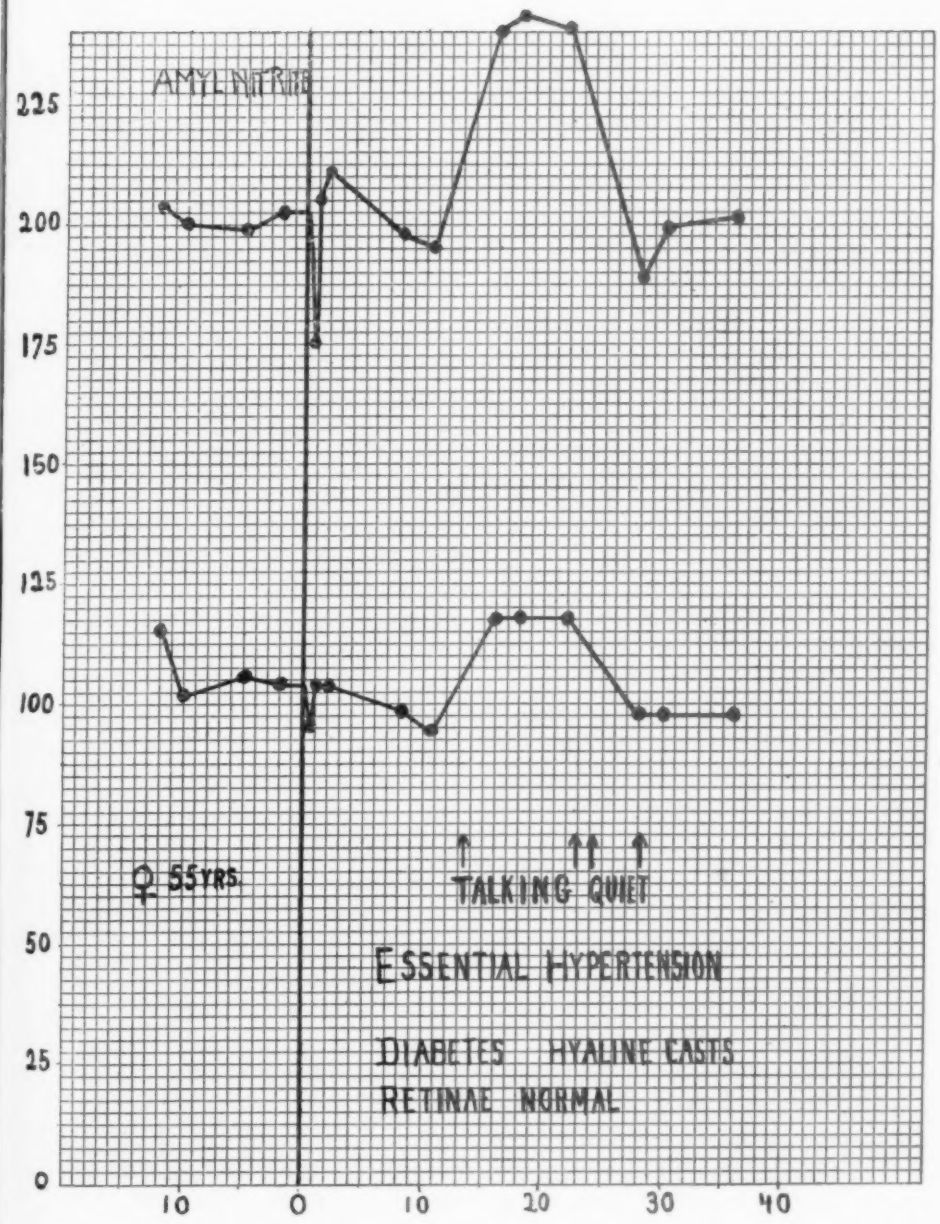

CHART 8. Arterial hypertension. Note effect of animated conversation on blood pressure.

any drop in diastolic pressure had been noted, and was well established before any effect more than a five mm. drop had been observed even on the systolic pressure. (See Charts 10, 11 and 12.) In one instance complete relief had occurred when both systolic and diastolic pressures were within 5 mm. of the point at which they were first observed (Chart 10) and in another (Chart 14) no drop whatever but an actual rise in diastolic pressure took place although there was at the time complete relief of the pain. (The shaded areas on the charts which are intended to indicate the degree of pain are based on the patient's answers to repeated questioning during the tests.)

(2) In the three attacks that were studied by the use of amyl nitrite the usual abrupt fall in 30 seconds followed by a quick rise in a minute and a half was found. In two instances the pressure remained for the next twenty minutes at a distinctly lower figure than before the administration of the drug.

Relief of Pain. In no instance did the relief of pain correspond to the low pressure reading. One patient in whom, as is shown in Charts 11 and 13, the pressure had fallen abruptly, a drop of 70 mm. systolic and 30 diastolic, stated that the pain had not changed in the slightest. Three seconds later sudden relief took place, as he said, "like pricking a toy balloon." On a second patient (see Chart 12) thirty seconds after amyl nitrite when a drop of 70 mm. systolic and 32 mm. diastolic had occurred, there had been no change at all in the intensity of the pain but at the end of one minute, although the diastolic pressure had returned to its former level of 110 mm. and the systolic had risen to 180 mm., or three-quarters of the way back to the starting point, the pain had markedly diminished and after two and a half minutes had completely disappeared although the pressure readings were at that time very nearly what they were before the inhalation of the drug.

Comment. It is evident from the above that the relief from pain experienced after nitrite therapy in angina pectoris is independent of the decrease in systemic blood pressure—diastolic or systolic. This certainly suggests that such relief is probably not due to nitrite dilation of the peripheral vessels. The only other known action of nitrites which could relieve the pain, then, is the action on the coronary arteries—and if increased flow through the coronaries is the mechanism of the relief, the cause of the pain must be an ischemia of the heart muscle. It is probable, then, that anything which causes an increase in the work of the heart such as excitement or exertion, with the known increase in peripheral blood pressure and heart rate which accompany them, causes in these patients a temporary ischemia of heart muscle. The underlying cause of the whole picture must therefore be deficient coronary circulation which is incapable of supplying the physiologic needs of the musculature of the heart during periods of stress.

In connection with the reaction of patients with angina pectoris to nitrite therapy brief reference will be made to one patient, a lady of 76 years of

CHART 9. Arterial hypertension. Composite charts. Lack of any definite effect of nitrites except the temporary response after amyl nitrite.

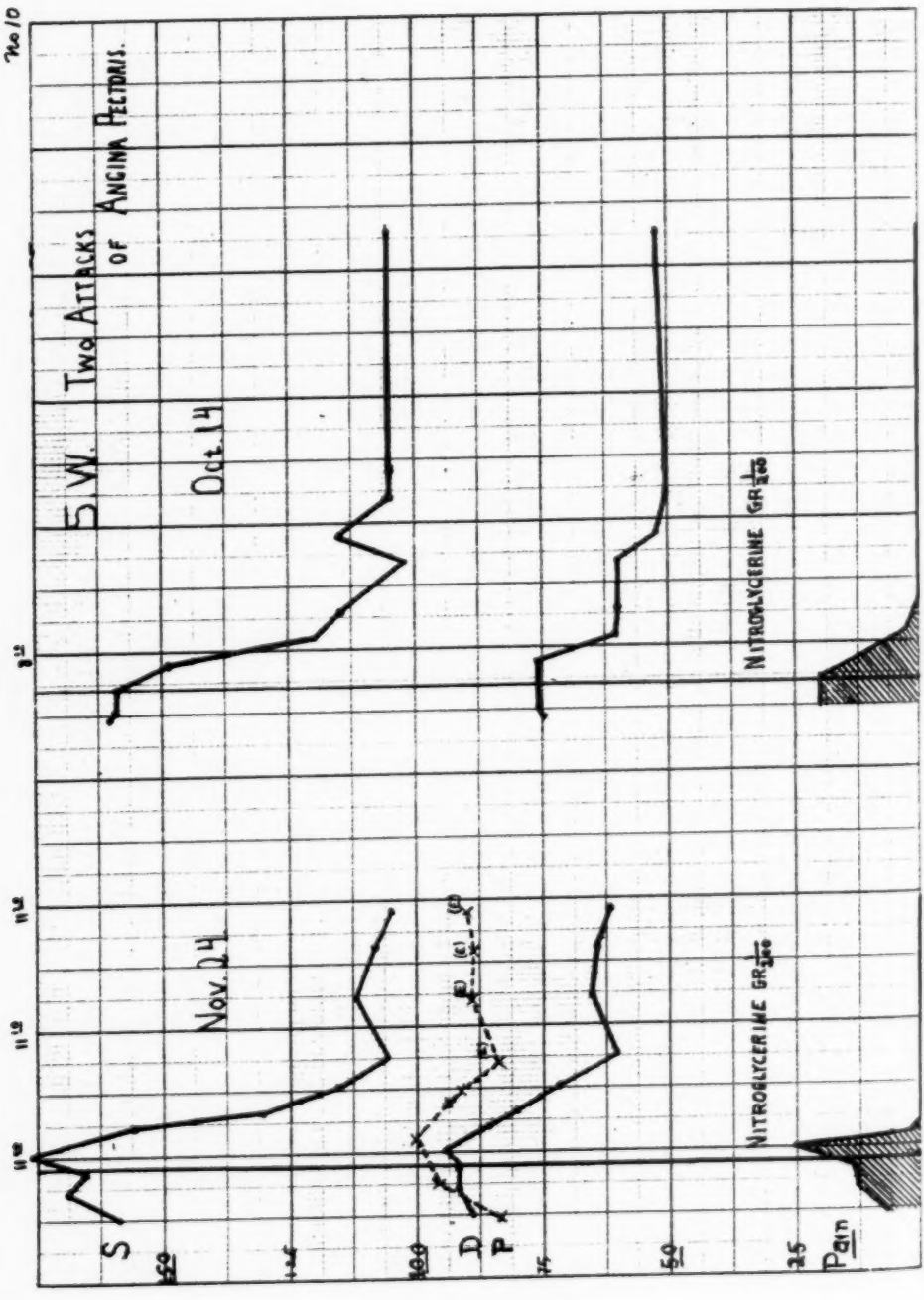

Chart 10. Angina pectoris. Response to nitroglycerine.

CHART 10. Angina pectoris. Response to nitroglycerine.

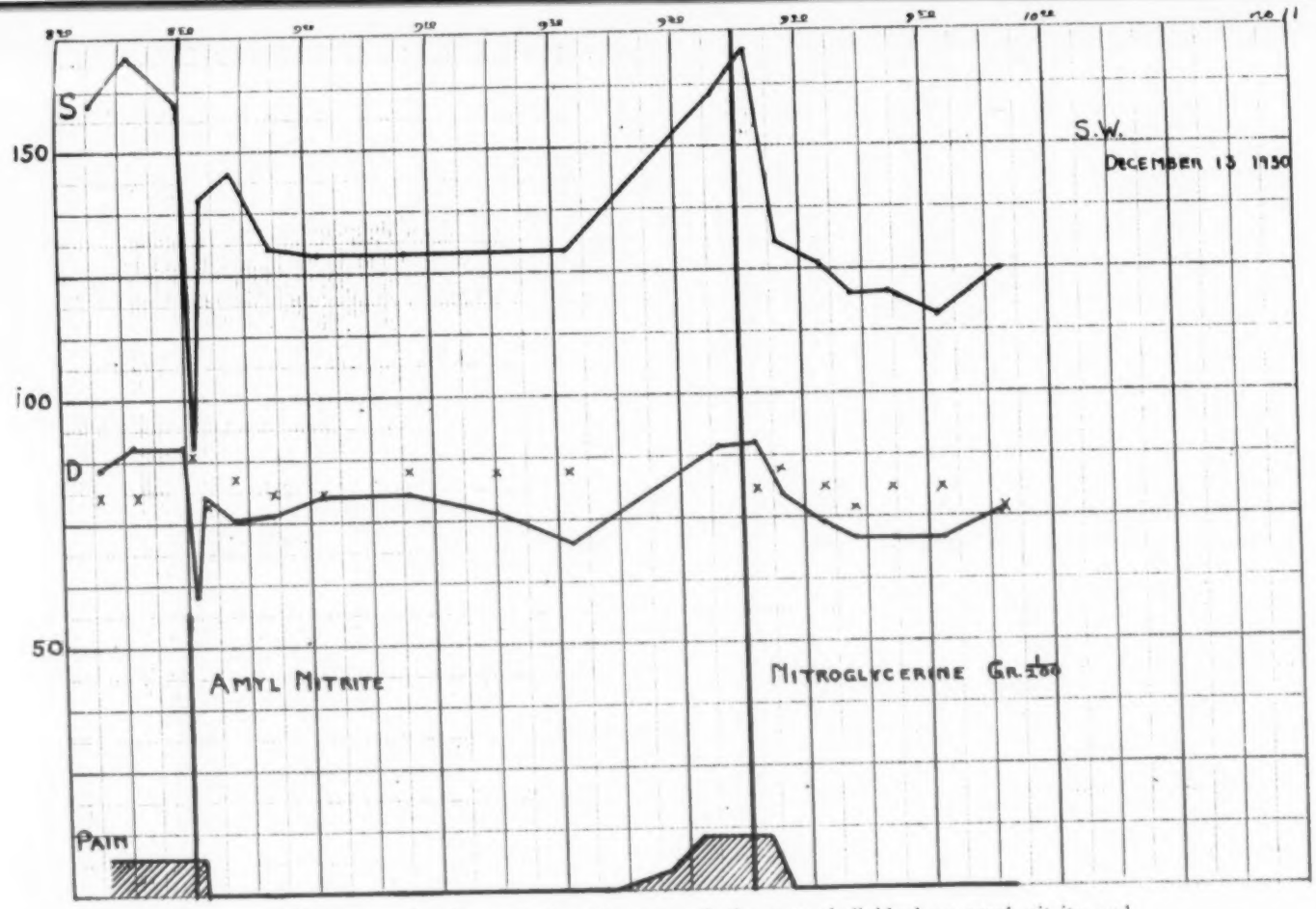

CHART 11. Angina pectoris. Response of the same individual to amyl nitrite and nitroglycerine in two attacks occurring within an hour.

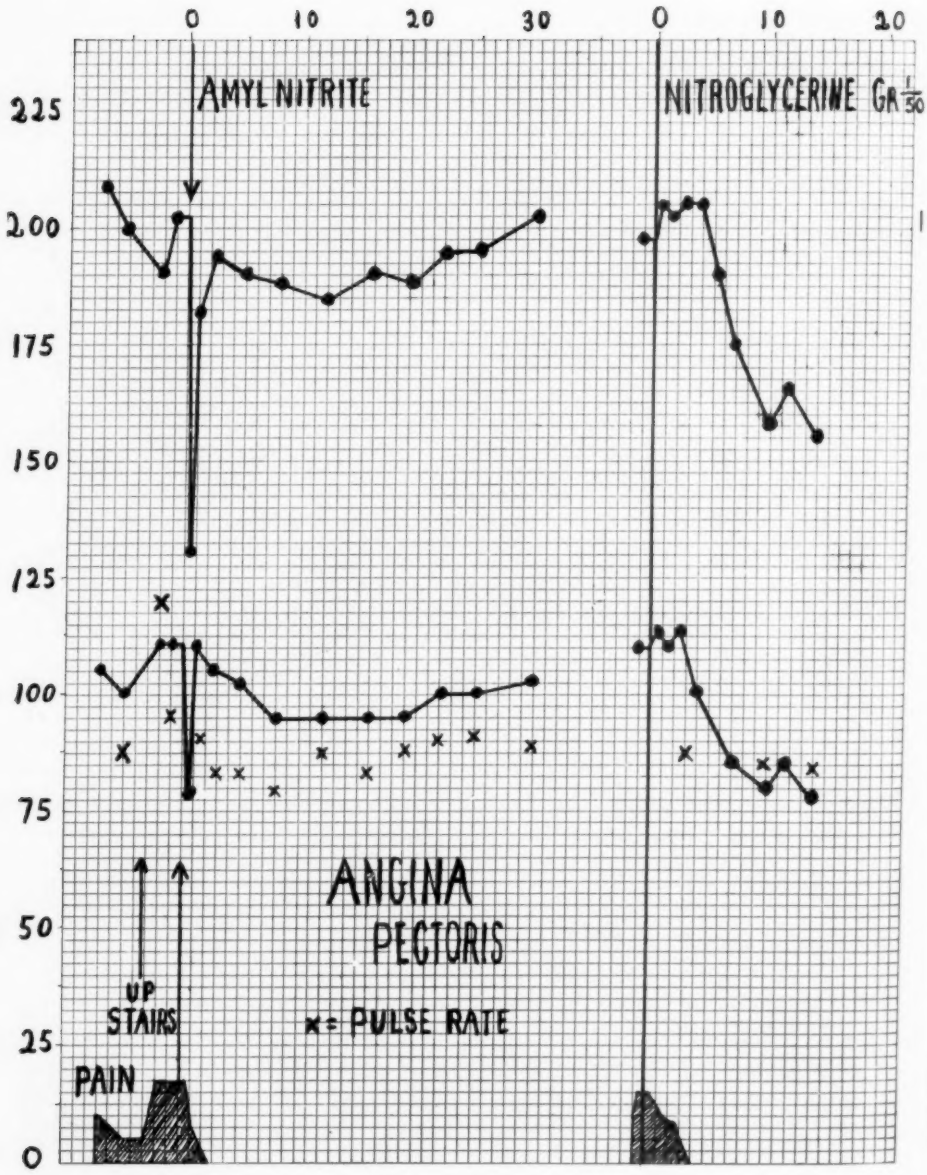

CHART 12. Angina pectoris. Response to amyl nitrite and nitroglycerine. Note lack of correspondence between pressure levels and pain relief.

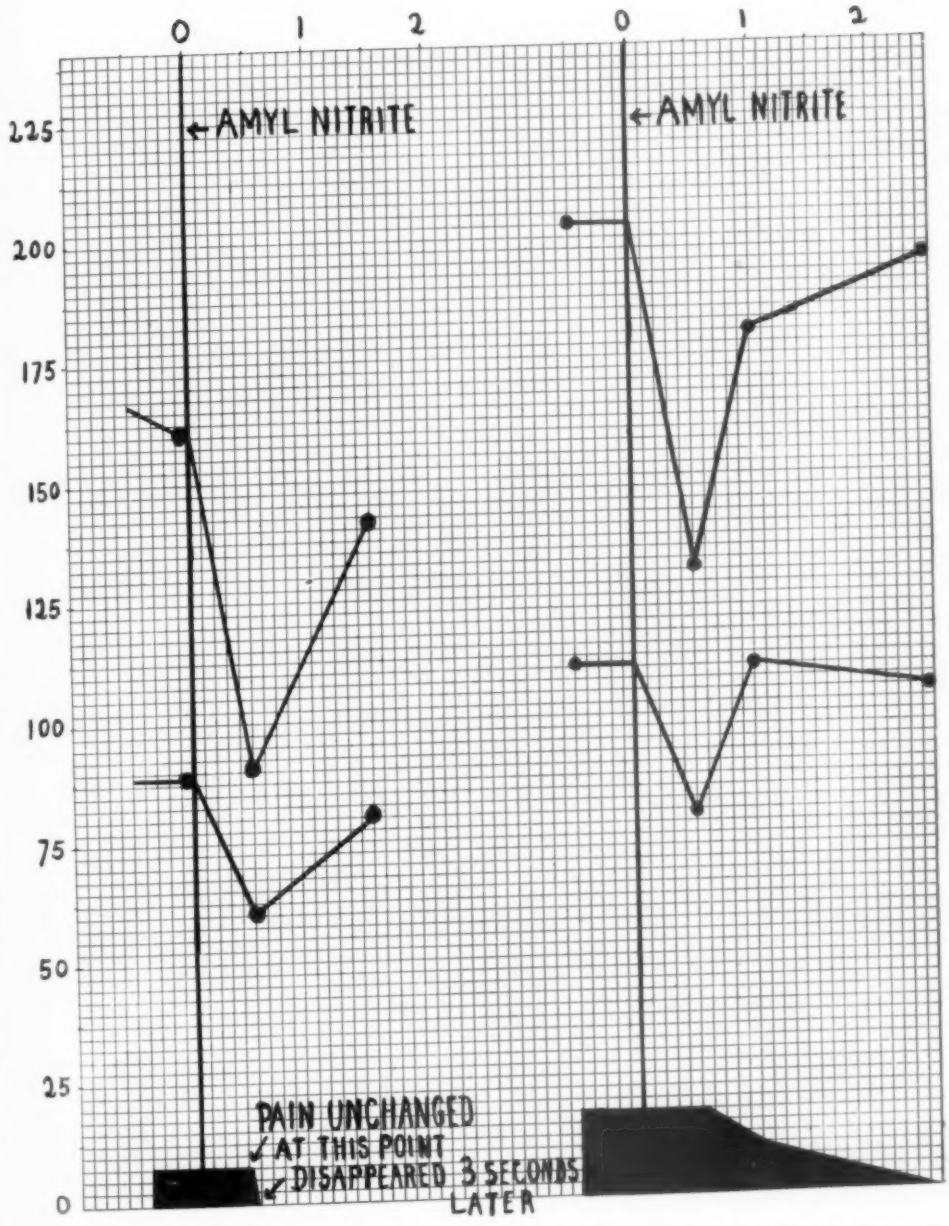

CHART 13. Angina pectoris. Chart of pressure curves and pain relief in cases illustrated in Charts 11 and 12 drawn to a different scale to show more clearly the lack of correlation between fall in pressure and pain relief.

age, in whom the administration of nitroglycerine gr. 1/100 per os because of anginal pain of moderate severity, was followed, after the usual relief had been experienced, by a recurrence of much more severe and viselike pain, sweating, pallor and a further marked fall in blood pressure (Chart 16.) All our clinical observations including electrocardiographic studies before and after the attack, confirmed the impression that while under observation the patient had suffered an occlusion of a branch of a coronary artery. This case will be reported later in detail. One certainly is led to suspect that in this instance the action of the nitroglycerine may have been a factor in bringing on or hastening the thrombosis of the coronary artery involved.

Summary

Studies of the rapidly acting nitrites, nitroglycerine and amyl nitrite, in the usual therapeutic doses, on normal people, persons suffering from arterial hypertension and from the anginal syndrome showed the following results:

1. The usual symptoms, tachycardia, flushing, headache, etc., varied greatly and appeared quite independent of pressure levels.

2. Normal human beings after the application of nitroglycerine by mouth or hypodermically showed no consistent change in diastolic pressure. The systolic pressure also underwent no consistent change although there was in some instances a slight tendency downward.

3. The reaction of normal human beings to amyl nitrite was a sharp fall in thirty seconds followed by a quick rise to above the previous level in about two minutes. Later blood pressure readings approximated the initial figures.

4. Patients with arterial hypertension with and without severe renal damage showed similar reactions. After nitroglycerine there were no consistent changes in either systolic or diastolic pressures. After amyl nitrite they showed a sharp drop in systolic pressure similar to that seen in the normal in the first half minute followed by a compensatory rise at times exceeding the former level. The diastolic pressure in some instances underwent a similar but less marked variation and in others almost none. Although the presence of a marked diastolic drop may indicate an early stage of arteriolar disease, as suggested by Stieglitz, it did not bear any definite relation to the presence or absence of sclerosis of the retinal arterioles in the patients studied. The rapidity of the drop and the compensatory rise made an accurate determination of the extent of the drop impossible.

5. In the presence of the anginal syndrome nitroglycerine caused a marked drop in systolic pressure within two to five minutes at times preceded by a slight rise in the first minute. The diastolic pressure usually but not always showed a fall also. After amyl nitrite the usual sharp fall in systolic and diastolic pressure occurred followed quickly by the compensatory rise. In both instances pain relief occurred promptly but was quite independent of pressure levels.

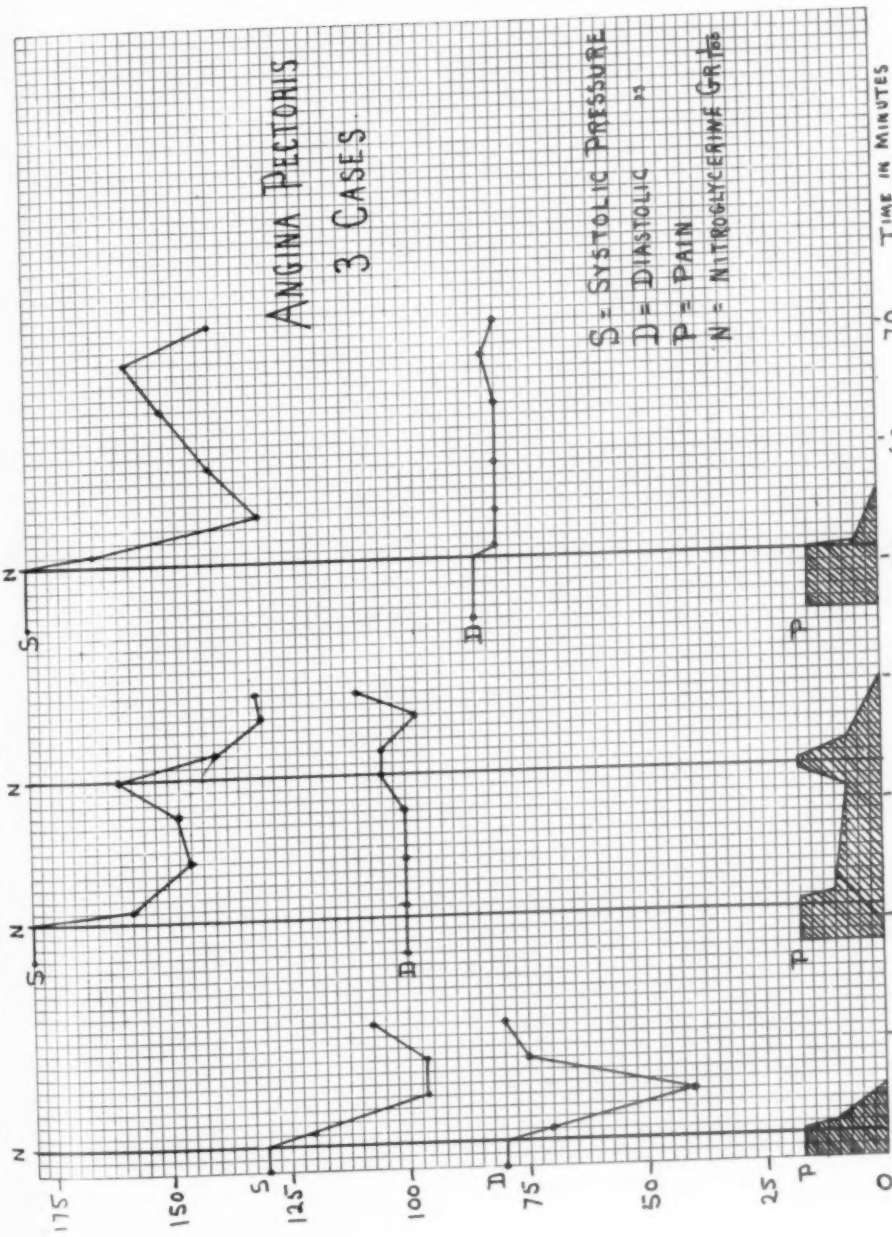

CHART 14. Angina pectoris. Response of three different individuals in attacks. Note absence of fall in diastolic pressure in second case in spite of complete pain relief.

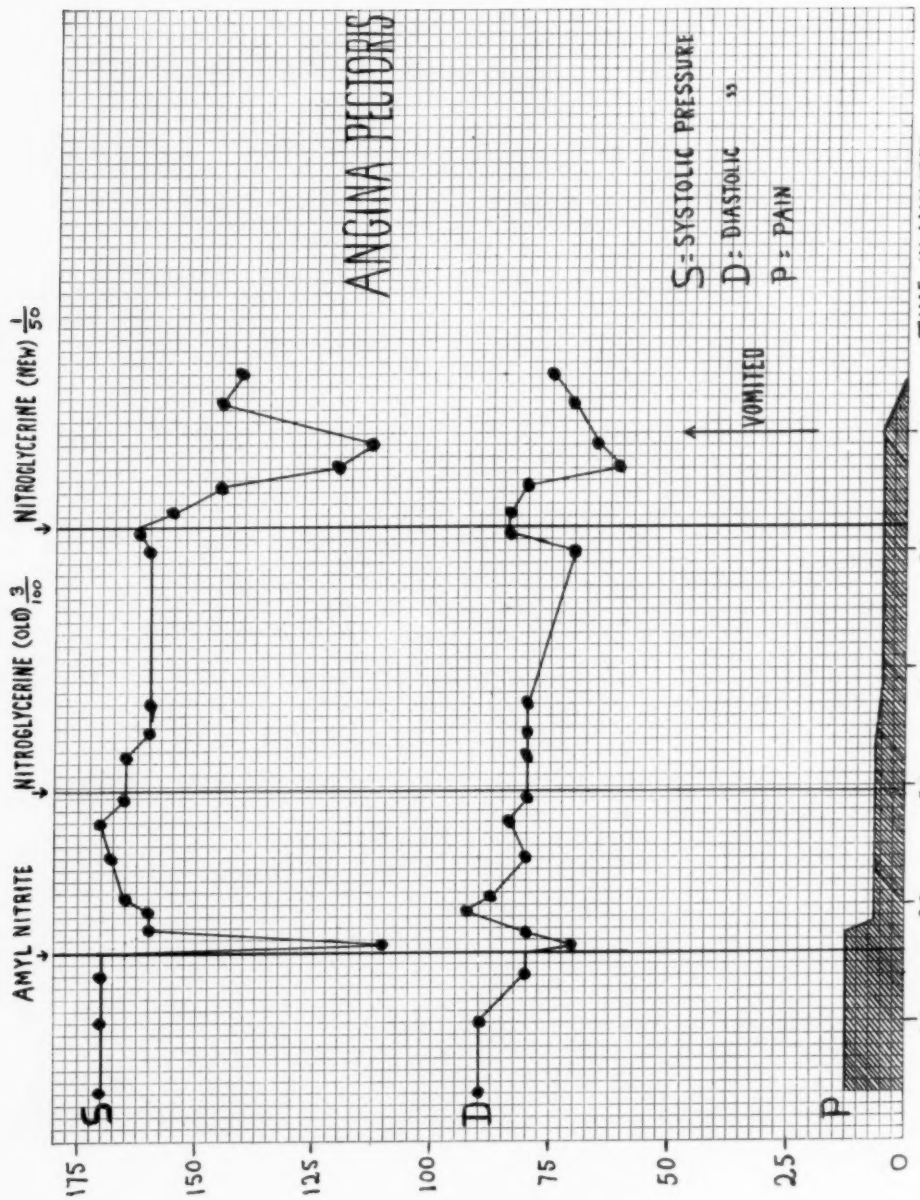

CHART 15. Angina pectoris—woman 76 years old who had previously had coronary occlusion illustrated in Chart 16. Note absence of response to tablets of nitroglycerine which had been kept on the bureau about a month—compared with response to new tablets.

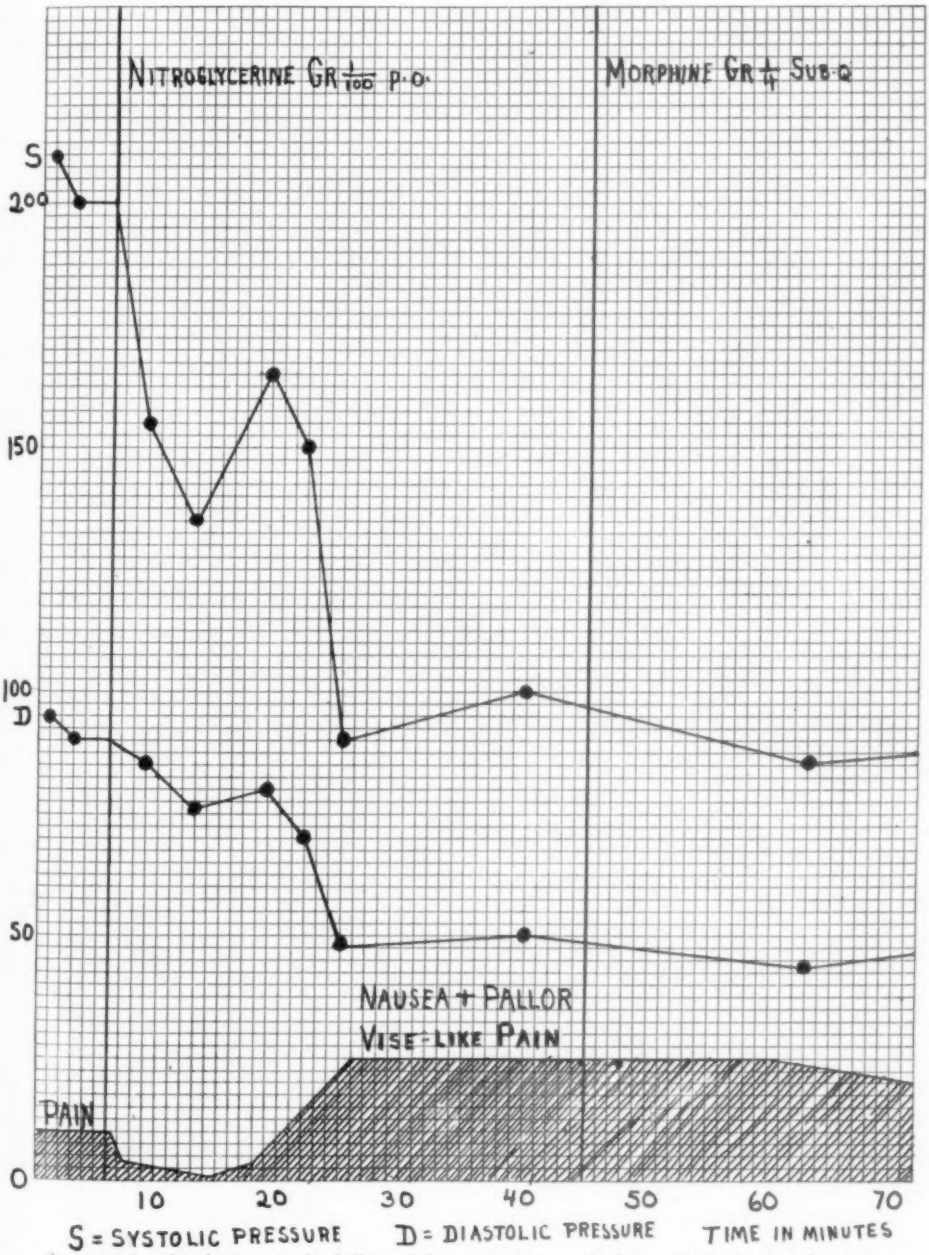

CHART 16. Angina pectoris followed by coronary occlusion. Note favorable response to nitroglycerine followed by return of severe viselike pain and a much more marked and permanent fall in blood pressure.

Conclusions

1. Except for a very transient fall in blood pressure after amyl nitrite, neither it nor nitroglycerine, when used in the usual therapeutic doses, causes any consistent blood pressure changes in normal human beings or in persons with arterial hypertension with or without severe renal damage or retinal arteriolar sclerosis.

2. The fall occurring after the use of amyl nitrite is so rapid and transitory and so independent of subjective symptoms, that it is impossible to measure it accurately by taking blood pressure determinations in the ordinary way. This fact greatly decreases its usefulness as a test for arteriolar relaxability in estimating the prognosis in arterial hypertension.

3. In persons suffering from attacks of angina pectoris of the usual ambulatory type, a rapid fall in systolic and usually in diastolic pressure takes place after the use of these drugs.

4. The pain relief which occurs in these cases of ambulatory angina is independent of the pressure levels and therefore apparently independent of the action of the nitrites on the peripheral vessels but due to their action in increasing coronary circulation.

5. The cause of the pain in ambulatory angina is probably an ischemia of the myocardium dependent upon an insufficient blood supply due to disease of the coronary arteries.

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Auricular Flutter and Complete Heart Block: With Restoration of Sinus Rhythm and A-V Conduction*

By Leslie T. Gager, M.D., *Clinical Professor of Medicine, George Washington University, Washington, D. C.*

NEITHER auricular flutter nor complete heart block are by themselves extraordinarily uncommon and it is safe to say that they would be even more familiar were the presumptive signs and symptoms of each borne in mind and the means taken for definitive diagnosis. The coexistence of these two disorders of the heart beat, however, is a clinical rarity. Previous to the example which is here reported, I find in the literature a total of fifteen cases of auricular flutter occurring in the presence of total auriculo-ventricular block, while in two patients only, those of Schott[6] and of Gallemaerts,[11] was there the joint restoration, under treatment, of sinus control and A-V conduction.

Case Report

N. R., a negro laborer aged 70 years, worked until the day before his admission to the George Washingon University Medical Service, Gallinger Municipal Hospital, on Jan. 20. His complaints were increasing shortness of breath and swelling of the ankles.

The family history was irrelevant and the patient had never been seriously ill. Venereal infection was denied and he had been moderate in the use of alcohol and tobacco.

His present illness began three weeks before admission with chills and fever and a dry cough, followed by dyspnea on effort, occasional palpitation and slight edema. He was able to sleep comfortably, his appetite and digestion were good, the bowels were regular and there was total absence of pain, fainting or convulsions.

The physical examination showed a well-developed, sparely nourished old man lying flat in bed. Respirations were 16, regular and quiet. The jugular veins were not distended.

The pupils were active and the knee jerks present.

The retinal vessels were found without notable changes, the peripheral arteries were markedly sclerotic.

The apex of the heart gave its impulse in the sixth interspace 10 cm. to the left of the midsternal line. Apex and pulse rates were 44 per minute, the rhythm was regular. The blood pressure was 122/78. Clear heart sounds coincided with the apex rate, no intervening sounds were made out. The chest was full and the lungs were moderately emphysematous. There were numerous râles at the bases.

The liver edge was at the costal margin, not tender and the wall of the abdomen was relaxed.

Pitting of the ankles was present.

The urine showed a specific gravity of 1.022, a faint trace of albumin and an occasional hyaline cast. Hemoglobin was 70 per cent, white blood cells 7,000; with poly-

*Case presentation at clinic for the American College of Physicians, George Washington University Hospital, March 28, 1931.

morphonuclears 53, band forms 12, large mononuclears 5, and lymphocytes 30 per cent. There was a one plus Wassermann reaction of the blood.

A teleroentgenogram gave an aortic diameter of 7.4 cm., and the transverse cardiac diameter 16.1, with a thoracic width of 30.0 cm.

The electrocardiogram (figure 1) confirmed the clinical diagnosis of complete heart block, with a ventricular rate of 44 beats per minute, and in addition it disclosed the presence of auricular flutter at 274 beats per minute.

The course of the patient was afebrile, the apex and pulse rates ranged from 42 to 52 per minute and respiration from 16 to 20.

Treatment at the outset, in the presence of congestive heart failure, consisted in rest in bed. This was supplemented by full doses of digitalis, and in the 12 days from Jan. 21 to Feb. 2 the patient received 960 minims (62 cc.) of standardized tincture, without apparent effect either on the flutter or on the block. The flutter varied from 280 beats to 260 beats per minute. Beginning Feb. 2 the digitalis was discontinued for one week without change in auricular or ventricular rate and was resumed from Feb. 9 to Feb. 16, at 60 minims (4 cc.) per day, also without effect.

Quinidine sulphate was prescribed on Feb. 16, in doses of 0.4 gm. (gr. vi) given three times daily.

On the first day of its administration, there occurred what the patient described as a "shaking spell all over" which lasted three hours and was without fever. Subsequently, the pulse and apex rates were found from 60 to 70 beats per minute, with a dominant regularity frequently broken by beats which were interpreted as premature. The electrocardiogram taken on Feb. 24 (figure 2) shows the persistence of this arrhythmia and its nature. There has been a return to normal sinus rhythm, most clearly seen in Lead III. Lead II shows a period of auricular silence—sino-auricular block?—followed by ventricular escape.

As quinidine was continued the ventricular rhythm became entirely normal and on March 15 the drug was discontinued. On March 21, the electrocardiogram (figure 3) reveals normal sinus rhythm, and its control of the ventricles. The same prolongation of

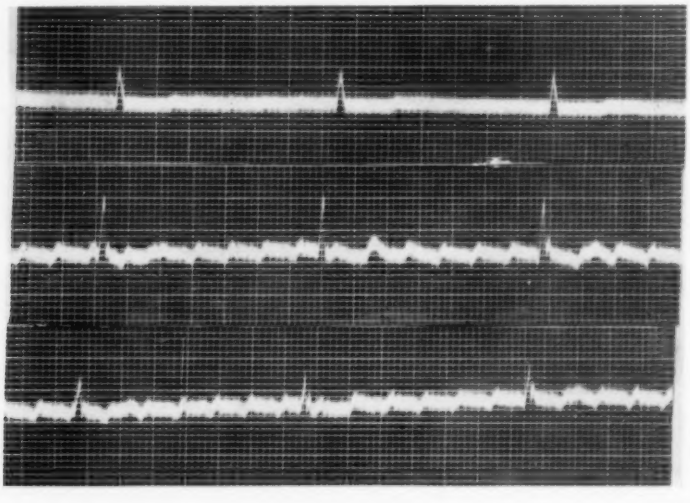

FIG. 1. Auricular flutter, rate 274; complete heart block; ventricular rate 44. Supraventricular type of QRS indicates origin in bundle. (Electrocardiograms by G. Edward Smith.)

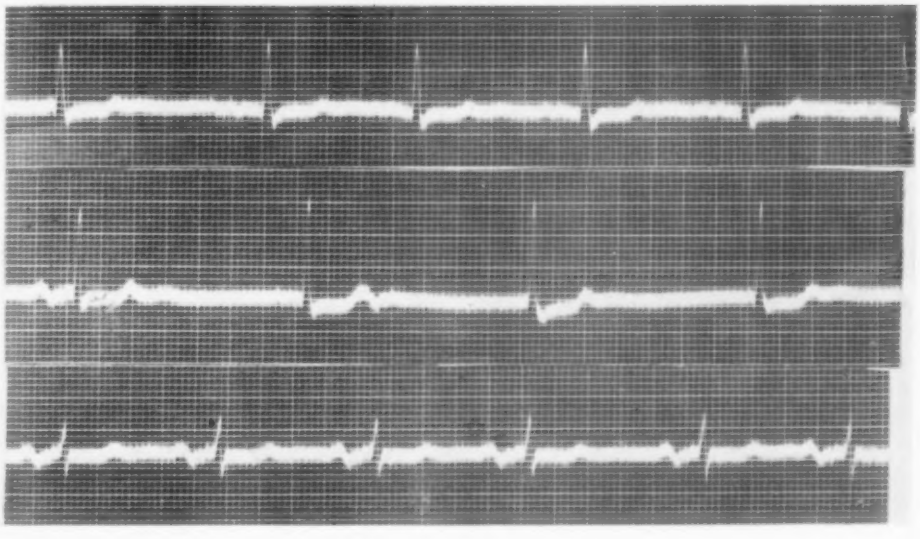

FIG. 2. The response to quinidine. Lead III best shows normal sinus rhythm and control of the ventricles. P-R interval is 0.24 sec. Lead II shows a transitory phase with auricular silence and ventricular escape. The change in amplitude of the QRS waves is distinct.

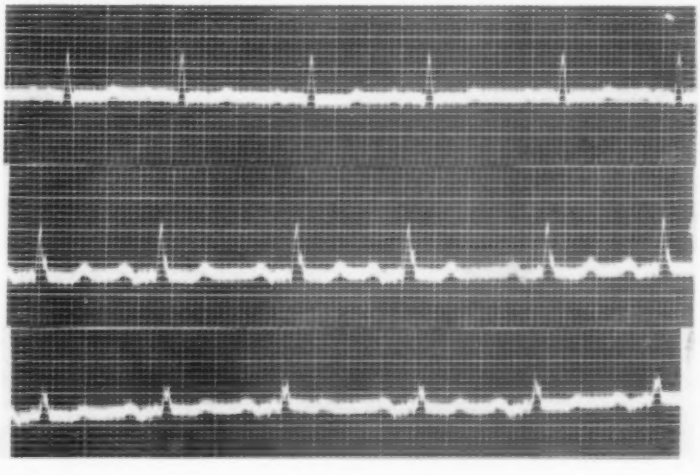

FIG. 3. Complete restoration of sinus control, but persistence of delayed A-V conduction. No quinidine has been given for one week and no digitalis for five weeks. The QRS groups in II and III have decreased in amplitude and show notching.

the P-R interval to 0.24 sec. which was noted on Feb. 24 is still present. (For over a month, no digitalis has been given.) The QRS complex occupies 0.08 sec., but is somewhat slurred and split. The T wave is upright in all leads. The rate in this record is 82.

On March 25, an occasional prolonged pause and then a beat suggested the return of ventricular escape. Quinidine was resumed, and upon discharge March 28, the rate was 72 to 76, the rhythm regular.

The mental as well as the physical improvement of the patient under treatment is of interest. It was noted at the time of admission that the patient was cooperative but his mind was dull and blurred and his responses sluggish. He became ambulant after the first week, except during the first few days of quinidine therapy, but there is a note on Feb. 25 that there is marked improvement in the mental condition along with the restoration of the normal heart rate.

In summary, a man with arteriosclerotic heart disease, without cardiac hypertrophy or evidence of pre-existing hypertension, and without the history of Adams-Stokes attacks, suffering from congestive heart failure, showed complete heart block, and by electrocardiographic demonstration, auricular flutter. The auricular rate ranged from 260 to 280, the ventricular from 42 to 50, in the electrocardiograms. Full doses of digitalis were ineffective but quinidine had a prompt action in abolishing flutter and restoring normal sinus control and heart rate. A prolongation of A-V conduction time persists and there is further evidence of myocardial disease in the distortion of the QRS complex.

Review of Literature

It is noteworthy that clinical knowledge of auricular flutter begins with a patient whose complete heart block furnished the incentive for further graphic study and then facilitated the analysis of the rapidly and regularly occurring "a" waves in the polygram.

This patient of Ritchie's[1] was a man of 55. He came under observation with a pulse rate of 36 and a history of shortness of breath and attacks of faintness and giddiness since pneumonia six months before. The blood Wassermann reaction also was positive. After a period of normal auricular action, in June, 1905, flutter at 274 beats per minute was discovered. Observations were continued over a period of nine years.[2,3] At first paroxysmal or intermittent, the flutter became persistent in 1908. The ventricular rate ranged from 32 to 36, was occasionally elevated by premature beats and during one period showed groups of rapid beats (41 per minute). For two periods only, in 1913, did the auricular rate drop to normal, once after strophanthin and digitalis. The Adams-Stokes attacks ceased after the establishment of flutter.

In a woman aged 39 years, with rheumatic heart disease, Hertz and Goodhart,[4] in 1909, found auricular flutter persisting for ten months at a rate from 216 to 230, with a ventricular rate as low as 44, though usually higher, from 72 to 120.

A third patient was reported by Donzelot and Pezzi[5] in 1914, a woman of 62 years, whose auricular and ventricular rates respectively were 300 and 35 to 40.

Schott,[6] in 1920, discussing ventricular standstill and the Adams-Stokes syndrome, recorded these phenomena

in a woman aged 60 years who had had acute rheumatic infection six years before, and now showed runs of auricular flutter at 270 to 280 beats per minute and a ventricular rate sometimes in 4:1 ratio, during the course of which ventricular standstill was observed to occur, and sometimes independent ventricular rhythm at 58 beats per minute. Under digitalis the flutter merged into fibrillation and this into sinus rhythm, with recovery of excellent functional capacity. Repeatedly her life was saved, during the syncope of ventricular stoppage, by fist-blows over the heart.

Vinnis,[7] in 1921, reported a man of 68, with hypertension of 285/125 and no symptoms except vertigo, with respective rates of 240 and 35 for auricle and ventricle.

Syphilis and the precocious arterial degeneration due to it were held responsible by Arrillaga and Waldorp[8] for the aortic insufficiency and complete heart block in a man of 42 years. The ventricular rate was 25 to 29, the auricular tachysystole 225 to 260. No improvement resulted from active antisyphilitic treatment.

In 1922, Keating and Hajek[9] witnessed the onset of flutter during her hospital stay in a woman aged 50 years who for four years had suffered from attacks of collapse and momentary unconsciousness. On admission, examination and electrocardiogram showed a simple tachycardia, rate 140. A week later, there occurred auricular flutter, rate 360 and complete block with ventricular rate 30. The auricular beats were audible. Later records showed a normal auricular rate, still later impure flutter and fibrillation with many premature ventricular beats.

Wiltshire,[10] in 1923, made particularly interesting observations in the case of a man of 63 years suffering from complete heart block, and periods of ventricular standstill lasting up to 67 seconds and occasioning severe Adams-Stokes attacks. During some of these periods of ventricular silence, auricular flutter was present; in others, sinus rhythm; in still others the auricles also were completely silent—in one record for 13 seconds during the attack and for four seconds after. It was observed that the auricular rate during one episode of ventricular standstill fell from 240 to 165; this slowing was considered evidence of exhaustion of the auricular muscle, presumably from lack of blood supply; for after the ventricles again began beating, the auricular rate rose at once to 214.

The patient of Gallemaerts[11] was a man of 62 years. There were attacks of asystole; the electrocardiogram disclosed ventricular bradycardia, complete A-V dissociation and auricular flutter. The use of quinidine caused reversion of the flutter to sinus rhythm, and made manifest a delay in conduction both in the main bundle and one of its branches. The syncopal attacks ceased.

Hall[12] found a history of bradycardia and fainting in a man of 62 years who sought treatment for intermittent claudication. The auricular rate was 270, ventricular rate 42. Right bundle branch block was present.

Willius,[13] in 1927, described auricular flutter in a man of 50 with arteriosclerotic heart disease and congestive

failure. Complete block had been established for five years. The rates for auricle and ventricle were 236 and 36. Digitalis was not used in this patient, and quinidine had no effect. This was the only example of the occurrence of auricular flutter with complete block in 168 cases of flutter discovered in the routine electrocardiography of 40,000 patients.

Auricular flutter supervening in a woman of 50 years whose complete block had been observed for 11 years and whose history of slow pulse went back 20 years before this, was reported by Strauss[14]. The inciting cause of the flutter appeared to be a toxic adenoma of the thyroid. Two months after thyroidectomy the rapid jugular pulse disappeared and the electrocardiogram confirmed the return of sinus rhythm. The block persisted.

In the course of their large experience with flutter, Parkinson and Bedford[15] encountered a man aged 74 years with congestive failure and slow pulse of two years' duration. The auricular rate was 270, the ventricular, 35. Under digitalis, the flutter was converted to fibrillation and two days later sinus rhythm was restored. The complete block remained. During flutter the auricular sounds were clearly audible at the apex; under sinus rhythm the auricular sounds were again heard but not so loud as with flutter.

Henderson and Rennie[16] reported auricular flutter with full heart block in a man aged 73 years who complained of weakness, fatigue and epigastric fulness. The auricular rate was 294 and that of the ventricles 28 to 34. Atropine brought a slight increase in ventricular rate but both conditions persisted and the patient died three months later.

Finally, in 1930, Lian and Viau[17] recorded their observations in a man of 54 years who came under treatment in 1927 for a complete block, with attacks of ventricular standstill and syncope, which disappeared under antisyphilitic measures. In January, 1929, there were found complete heart block and right bundle branch block, auricular rate 84, ventricular rate 25. In April, 1929, the electrocardiogram showed flutter, at a rate of 242, ventricular rate 32 and left bundle branch block. In May 29, following 2.5 mg. of digitalin given over six days, the flutter disappeared, the complete dissociation remained, and the right bundle branch block reappeared.

Criteria for Diagnosis

When auricular flutter occurs singly, its presence is suggested by a regular persistent pulse of 120 to 170 beats per minute. The diagnosis becomes reasonably certain if the pulse suddenly doubles in rate. In other words, a 2:1 or 3:1 A-V ratio is suddenly converted to 1:1 rhythm. But when transitions from one to another ratio are occurring frequently the pulse may not be regular; in the presence of the slower auricular flutter rates or of the higher auriculo-ventricular ratios, the rate of the ventricles may not excite attention. For these and other reasons—such as the inconstant effect of vagus (carotid sinus?) pressure or of digitalization—recourse must be had to the electrocardiogram.

As far as complete heart block alone is concerned, the idioventricular

rate is usually below 50 beats per minute and clinical diagnosis becomes the more assured as the rate falls to 40 and below. But total dissociation between auricle and ventricle is by no means stable: the ventricular rate, as in an aged physician under recent observation, may rise from 39 to 76 beats per minute, or the regular rhythm may be interrupted by ectopic ventricular beats or psychic influences and even changes in posture[18] may produce the most striking changes in impulse conduction. In block, therefore, as in flutter, the evidence of the electrocardiogram is indispensable.

When, now, the two disorders of the heart beat are superimposed, the peripheral signs, such as apex and pulse rates, and the evidence of circulatory embarrassment, either transient in the form of Adams-Stokes attacks or in the more persistent congestive failure, are dominated by the block and ventricular insufficiency. Evidence of flutter must be sought in the way of abnormal auricular pulsations in the jugular veins or abnormal auricular sounds on auscultation either over the heart or over the jugular bulb. Fluoroscopy may disclose the auricular rate. But since these phenomena commonly are difficult, if not impossible, to elicit, once more the graphic methods must be looked to for an assured diagnosis.

Physiological Considerations

Without entering upon any extended discussion of the functions of heart muscle, particularly the properties of irritability, conductivity and rhythmicity which are especially concerned in the physiology of flutter and complete block, it is possible to divide these cases into two groups.

In the first group are those in which the A-V dissociation was established prior to the onset of auricular flutter. Here perhaps the two disorders may be regarded as coincident in the course of progressive myocardial structural change: a definite interrelationship is lacking.

On the other hand, if flutter precedes, the possible effects of the rapid auricular impulses upon the capacity of the bundle for conduction or of the ventricle for excitation are to be considered. In experimental heart block Erlanger showed how increased auricular rate brought increase in the degree of dissociation; recently Herrmann and Ashman[19] have discussed the mechanisms that may underlie both the gradual and the acute onset of complete block as well as of bundle branch block.

Certainly in the case which is here reported, as in the patients of Gallemaerts and Schott, the restoration of normal sinus rhythm would seem to have removed the factor of fatigue of the main bundle and thereby to have influenced the return of A-V conduction. In Lian and Viau's case the influence of flutter on bundle branch block is of interest. Parkinson and Bedford ascribe the 2:1 and 4:1 ratios (persistent 3:1 ratios are exceptional) to defective conductivity in the presence of flutter, the functional nature of which is shown by normal conduction when sinus rhythm returns.

The bearing which these facts have on treatment is that they suggest the importance of attempting, either by

digitalis or by quinidine or both, to restore sinus rhythm with the possibility of influencing A-V conduction.

SUMMARY

A patient with auricular flutter coexistent with complete heart block was restored to sinus rhythm and A-V conduction by the use of quinidine sulphate. Physical and mental improvement resulted.

Fifteen cases have been found in the literature showing the association of auricular flutter and total block and the clinical phenomena and criteria for diagnosis are reviewed.

From experimental and clinical observations in partial block and from the results in three cases of complete block, the value of restoring sinus control in cases of auricular flutter is shown.

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Primary Aplastic Anemia; A Discussion and Report of Two Cases*†

By James B. Carey, M.D., F.A.C.P., and Joseph H. Taylor, M.D.,
Minneapolis, Minn.

THERE are various toxic and chemical agents, which may so affect the bone marrow that it is incapable of forming blood elements, and a condition of profound anemia may therefore occur. Infectious diseases, which progress to severe stages of toxicity or septicemia; benzol; trinitrotoluene; arsenic; roentgen rays and radium emanations can all affect the hematopoietic system in such a manner as to produce the clinical picture of an aplastic anemia. In certain chronic blood disorders and malignancy, there often occurs an exhaustive aplasia of the blood-forming tissues.

Excluding all known etiologic factors, however, there remains the primary or idiopathic case. Ehrlich[1] first described such a clinical entity in 1888. Since his report other terminology has been suggested. Pappenheim[2] suggests "a-regeneratory anemia" and later Schneider[3] suggests "toxic paralytic anemia" or "toxic anhemopoietic anemia". However, since at autopsy these cases show a completely aplastic condition of the bone marrow, a hypoplasia so profound that not even the normal amount of blood elements is found, with little hint as to the possible cause, it would seem that Ehrlich's original term is the most applicable. Any other designation implies etiologic factors, and none has been known.

Aplastic anemia patients are usually young adults or individuals of early middle age, in fair state of nutrition, showing pallor of either grayish or yellowish tinge, with hemorrhages into skin and mucous membranes. There is usually stomatitis and glossitis, progressing often to an extreme phlegmonous induration or gangrenous slough, and a septic type of temperature which may be due to the mouth lesions, especially as they usually become secondarily infected.

Further study of the case should reveal these other positive data:

1. Extreme anemia (counts as low as 500,000 or less with hemoglobin often too low to read accurately.) The anemia is of the hypochrome type with no evidence of blood regeneration.

2. Leukopenia which also may be very low (1,000) with a relative lymphocytosis.

3. Thrombocytopenia; platelets may be too few to count accurately; usually less than 75,000.

*From the Department of Medicine, The Nicollet Clinic. Read before the Minnesota Society of Internal Medicine, April 13, 1931.
†Received for publication, April 14, 1931.

Pathologically, there is found an extreme hypoplasia, or aplasia of the bone marrow. The marrow grossly is soft, yellow and almost completely replaced by fat. The microscope confirms this gross appearance of inactivity by revealing extreme hypoplasia or complete aplasia of cellular structures.

The outcome of all cases is fatal and no treatment up to the present time employed has been of the slightest avail.

Hirschfield[35] gives a complete bibliography up to 1911.

Sheard,[4] in his monograph on pernicious anemia and aplastic anemia, has covered the bibliography up to 1923 and discovered about 125 authentic cases. Since 1921 there have appeared in the literature reports,[5-24] presenting about twenty further adult cases. Schneider[3] mentioned sixty cases found up to 1918. There are several discussions of primary aplastic anemia based upon an indeterminate number of cases[25-33]. Many of these cases and discussions are in inaccessible literature; those papers found dealing with various phases of the subject are sometimes indefinite as to the actual number of cases on which the discussions are based. It may be estimated with reasonable accuracy, however, that not over 150 cases of primary aplastic anemia so far have been reported. A few cases reported among children were rather obviously anemias of hemorrhagic and aplastic type, following directly as the result of severe infections, and must therefore be excluded when considering only idiopathic cases. Some of Sheard's mentioned reports are of this category. There are many cases of pernicious anemia reported with so-called aplastic tendencies, meaning that there may be a stage in pernicious anemia when the bone marrow becomes aplastic, all blood elements consequently becoming reduced; hemorrhages occur and the patient dies.

The diagnosis of primary aplastic anemia is, in fact, often difficult and lies somewhere among several conditions; hemorrhagic and aplastic type of blood reactions occurring secondarily to sepsis, infection, sudden grave hemorrhage, pregnancy, poisons (benzol, trinitrotoluene, arsenic) and exposure to x-ray and radium. No difficulty is encountered if the primary agent can be determined. There are four diseases, however, which may cause confusion; thrombocytopenic purpura, pernicious anemia, aleukemic leukemia and agranulocytic angina. In leukemia, even in the aleukemic stage, there will probably be adenopathy and splenic enlargement and certain characteristic elements in the blood picture. The anemia will probably not be so profound, nor will the hemorrhagic features be so abundant or severe.

In pernicious anemia the history is usually of much longer duration and contains references to gastrointestinal symptoms, paresthesia and glossitis. There are evidences of hemolysis in skin, urine, duodenal contents, blood serum and feces. The anemia in pernicious anemia is not so profound until the end stages at least, nor are the hemorrhagic features prominent, although often present. In pernicious anemia there is also constantly present an achlorhydria and usually evidence of subacute combined degen-

eration (posterolateral sclerosis) of the spinal cord. The platelet count is not likely to be so completely reduced, nor is there such a marked leukopenia. The anemia is of the hyperchrome type.

In thrombocytopenic purpura the hemorrhagic features are more marked, and the anemia and leukopenia less so than in aplastic anemia. The morphology of the blood elements is practically normal.

Agranulocytic angina is a condition in which a severe gangrenous stomatitis develops and is accompanied by a blood picture of complete or almost complete absence of granular (polymorphonuclear) leukocytes. The red blood cells and hemoglobin may remain within normal range. The patients are usually middle aged females, and the disease is rapidly fatal (within two weeks ordinarily). There is, on account of the relatively normal hemoglobin and red count, no pallor, and the hemorrhagic features are usually absent. Piney has mentioned the agranulocyte reaction as sometimes occurring in aplastic anemia, but none of the formally reported cases have shown such phenomena.

Pathologically, the differentiation is not difficult from an examination of the bone marrow alone[34]. In aplastic anemia a soft, yellow, fatty hypoplastic or aplastic marrow is evident; in pernicious anemia the red marrow is increased, and shows hyperplasia. In thrombocytopenic purpura there is also a red, cellular marrow with an increase of blood elements and decrease of fat. The degree and kind of hyperplasia is not, however, that of pernicious anemia. In leukemia there is found a preponderance of lymphatic elements in the marrow. Further post mortem studies show in pernicious anemia the cord sclerosis or in leukemia the various characteristic glandular and splenic overgrowths. The bone marrow in agranulocytic angina does not show any characteristic changes of red cell elements, but granular cells are absent.

Two cases of idiopathic aplastic anemia are herewith described, and commented upon:

Mr. S. S., a farmer aged 33 years, a resident of Minnesota, consulted one of us (J.B.C.) on November 5, 1929, complaining of weakness and swelling of the abdomen. He said that in September, 1929, he first began to become easily fatigued while at his work. About this time he sustained a fall, bruising his left side, after which he noticed some abdominal swelling. His local physician told him he probably had some fluid in his abdomen. He became weaker from that time until consulting us, but did not lose weight. He had no gastro-intestinal symptoms other than a capricious and variable appetite and the feeling of distention. He had daily bowel movements, which retained a normal color and consistency. There were no urinary symptoms. His skin became pale and slightly yellow, but there was no itching. His tongue had occasionally been sore.

The only illness he had had in the past was an attack of pleurisy in 1924. His family history was negative.

Physical examination on November 5th showed a pale man, rather dyspneic on slight exertion, with abdominal distention. He was fairly well nourished, but of poor muscular tone. The skin and mucous membranes were very pale, and slightly yellow, but not jaundiced. The hair had begun to turn gray. The tongue was moderately atrophic, with a whitish area on the right side, the site of recent glossitis. The heart was normal, except for a systolic "hemic" murmur heard at the base. The lungs were clear. The abdomen was tympanitic, mod-

erately distended, but revealed no masses or other abnormalities. The liver was barely palpable at the right costal margin and seemed of normal consistency. The spleen was palpated with difficulty on account of the distention and was slightly tender. The reflexes were present and normal, and vibration sense over the inner malleoli as estimated by the "C" tuning fork was normal. There was slight edema of both ankles, extending one-third of the distance up the tibiae.

Gastric secretory analysis showed a complete absence of free hydrochloric acid with a total acidity of 27. Fluoroscopic examination of the stomach, after ingestion of a barium meal, showed a large atonic organ without defects. The barium filled bowel, by fluoroscope, was likewise atonic and contained much gas, but was otherwise negative. The urine was light amber in color, 1017 specific gravity and acid in reaction, with 2+ albumen, but no sugar. A few blood cells and an occasional hyaline cast were seen. There was a trace of urobilinogen and no urobilin. The blood serum bile index was 8 to 9. Blood Wassermann and Kahn reactions were negative. Blood pressure was 110/80. There was no lymphatic glandular enlargement. An examination of the blood showed coagulation time 4'15", bleeding time 12', and 50,000 platelet count. Hemoglobin was less than 10 per cent and the red blood cells numbered 500,000. There were 1,250 white blood cells with 64 per cent of polymorphonuclears, 23.5 per cent lymphocytes, 12 per cent monocytes and 0.5 per cent eosinophils. The polymorphonuclear elements showed a distinct shift to the left, with several young and immature forms. There were none of the so-called pernicious anemia neutrophils present. The smears of the red blood cells showed a distinctly aplastic tendency, with more anisocytosis and poikilocytosis than normal and only an occasional hyperchromatic or polychromatic cell; there was, however, no achromia. There was also an occasional nucleated red cell seen.

The patient was placed in the hospital and grouped for transfusion. He was found to be a Group IV with, however, rather atypical agglutination reactions to Group IV sera. A transfusion of 375 c.c. of citrated blood was given on November 6th. There was a moderate reaction about two hours following the transfusion, controlled by 10 m. adrenalin given by hypodermic injection subcutaneously. Liver extract (Lilly 343), 6 vials daily in orange juice, was begun and the patient placed upon the "Minot-Murphy" liver-containing diet.

The patient was given two other transfusions on the 9th and 17th, each followed by a very severe reaction, and neither of these additions of blood had appreciable effect upon the blood count, as even from the records below. A glossitis developed which became very severe, and spread onto the under surface of the tongue and to the buccal membrane. This lesion was undoubtedly responsible for the slight elevation of temperature noted constantly (100° to 101°, and at the time of transfusion reaction, 104° to 106°). Bleeding from the gums and rectum subsequently occurred; 50 c.c. of whole blood was used intramuscularly on two occasions, November 15th and 18th, in an unsuccessful attempt to control these hemorrhages. Petechial and purpuric spots appeared in scattered places over the body, and finally a day before death the surface of the abdomen was almost solidly covered with subcutaneous hemorrhages. The appetite remained good until the last two days, and the six vials of liver extract were continued until the last day. Death occurred November 27th, after a period of unconsciousness with elevated pulse (120), temperature (104°) and Cheyne-Stokes' respiration. An autopsy request was refused.

A few of the blood counts are herewith given (those showing transient effect of transfusion and whole blood injections are eliminated):

Nov. 7 Hgb. 20% R.b.c. 950,000
Nov. 11 Hgb. 10% R.b.c. 800,000
Nov. 16 Hgb. 12% R.b.c. 580,000 — no reticulocytes
Nov. 23 Hgb. 15% R.b.c. 520,000
Nov. 27 Hgb. 10% R.b.c. 450,000 W.b.c 8,600, no reticulocytes (This count was done just before death.)

Comment

The phlegmonous, almost gangrenous lesion of the tongue had been described in many of the other cases of aplastic anemia reported in the literature. The temperature also is a common finding in this type of anemia. Although the blood bile index was slightly elevated, there were no other very striking evidences of extreme blood destruction, such as are often seen in end stages or crises of true pernicious anemia. The bile pigments of the urine were normal, the stool was of normal color and neither skin nor sclera were at any time marked by jaundice.

The blood count was very low, and did not react to the stimulation of liver, liver extract, blood transfusions or whole blood injections. There was free bleeding from the gastro-intestinal tract and subcutaneous hemorrhage. There was an achlorhydria present, but no signs of combined cord sclerosis. There was an absolute leukopenia at the beginning. The terminal rise seen may have been the result of the transfusions and whole blood, or both. The history of the illness was of short duration and showed a rapid progression to the fatal termination.

The second case is that of a white male age 42 years. He presented himself to one of us (JHT) for examination on October 15, 1930, complaining of weakness, dyspnea and "anemia." About a month previous to this admission he had had a severe sore throat with fever, for which he remained in bed for two weeks. During this time he had palpitation, became weak, suffered dull headache and experienced occasional slight bleeding from the gums. These symptoms all continued and were still complained of when he consulted us. His family history was negative as to any anemia or other constitutional diseases. In the fall of 1929 he had had some epigastric distress and heartburn, for which he consulted a physician, who made a diagnosis of duodenal ulcer, and placed him upon diet and medical management. He obtained relief gradually from these symptoms, and had regained what he considered to be normal health at the time when he suffered the severe angina mentioned.

The original physical examination showed a fairly well nourished man of rather poor muscular tone. There was marked pallor of the skin and mucous membranes, but no jaundice. The pupils reacted to light and accommodation normally. The sclera were clear. There was moderate gingivitis at this time, but no stomatitis or glossitis. The tongue was not atrophic. The breath was foul, and there was hypertrophy of the tonsils with evidence of recent hemorrhage from the right one. The heart and lungs were normal. Neither the liver nor spleen were palpable. There were no masses, fluid or other abnormalities revealed by abdominal palpation. Deep reflexes and vibration sense were normal. Examination of the gastro-intestinal tract after ingestion of barium by fluoroscope was entirely negative. Urine examination revealed a specific gravity of 1013, acid reaction, no albumin or sugar, no bile or bile pigments. There were no casts, but an occasional red blood cell was recorded. Numerous stool examinations, made during his subsequent hospital sojourn, were negative for occult blood, parasites and ova. Blood Wassermann and Kahn reactions were negative. Gastric secretory analysis showed free hydrochloric acid 49, total acidity 69, blood bile index was 4 to 5. Examination of the blood resulted in the finding of a hemoglobin of 35 per cent (Dare), red blood cells 1,960,000, color index 0.92, white blood cells 2,100, polymorphonuclears 20 per cent, lymphocytes 75.5 per cent, monocytes 4.5 per cent. Bleeding time was 13 minutes and coagulation time 4 minutes, 45 seconds. The blood smears were essentially normal and remained so. The patient was hospitalized. The general hospital diet was ordered, and one ampule of Ventriculin was administered three times daily. The use of the Ventriculin was continued until the pa-

tient became too weak to eat or drink anything during the last two days of his life. During his stay in bed he gradually developed a stomatitis, which, as in the previous case, became very severe. Smears showed Vincent's organism and much secondary infection.

The patient was grouped and transfused twice, on Oct. 27 and Nov. 5. Following both transfusions, there were very severe reactions with chill and elevation of temperature. Just as in the previous case, these transfusions had no appreciable effect upon the blood counts, as seen by the following record: Oct. 22, hemoglobin 46 per cent (Sahli), red blood cells 2,000,000, white blood cells 8,000, no reticulocytes. Oct. 31, hemoglobin 47 per cent (Sahli), red blood cells 2,300,000, white blood cells 6,000. Nov. 4, hemoglobin 42 per cent (Sahli), red blood cells 1,650,000, white blood cells 6,000, no reticulocytes. The increase in the leucocytes was undoubtedly due to the mouth infection, and perhaps also influenced by the transfusion and continuing hemorrhages.

Fibrogen was given in one and two c.c. doses subcutaneously on numerous occasions in the last few days in an attempt to stop the hemorrhages, and on Nov. 6th 20 c.c. of whole blood was injected intramuscularly—all without effect on the bleeding.

During the seventeen days in the hospital, the temperature ranged from 98° to 104.8° F., the pulse from 76 to 116 and the respiration from 20 to 34. He suffered repeated, almost continuous, hemorrhages from the gums; was very uncomfortable on account of the stomatitis and finally after several large gastric hemorrhages, he died on Nov. 7, 1930.

An autopsy was performed on the same day by Dr. N. M. Levine of the Department of Pathology of the Medical School of the University of Minnesota from whose complete and detailed report the following positive and pertinent findings are taken: There were diffuse ecchymoses over the trunk, and also scattered petechiae over neck, chest and upper abdomen. There were also small petechial hemorrhages internally on the surface of the heart, pleural and peritoneal surfaces. The heart was otherwise normal and likewise the lungs, except for hypostatic congestion and edema of the latter. The liver was of a pale brownish red color. On opening the stomach, no ulcer was found, but submucous hemorrhages were numerous. The kidneys were normal, except for petechiae in the pelves. The spleen weighed 175 gm., and was normal grossly and in cut section. The bone marrow of the upper part of the femur was uniformly yellow and fatty; that of the ribs was yellowish pink. The anatomic diagnosis was primary aplastic anemia with multiple hemorrhages. The bone marrow, in microscopic section, showed marked hypoplasia of all elements and likewise a marked decrease of leucocytes was especially noted.

Comment

This case proved to be a primary aplastic anemia by autopsy findings and showed essentially the same picture and clinical course as the first one detailed. In this second case, the onset was precipitated by an infection—a severe sore throat. The course was practically the same in both cases, progressive weakness, multiple and repeated skin and visceral hemorrhages, the development of severe stomatitis, gangrenous in the first and complicated by Vincent's infection in the second. There was no stimulation of blood regeneration in either case by use of liver, liver extract or hog stomach extract. Injection of whole blood had no effect on the tendency to hemorrhage or the thrombocytopenia in either case.

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The Use of Sulphur for the Production of Fever in Peripheral Vascular Diseases*†

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THE artificial induction of fever as a therapeutic measure in peripheral vascular disease has been well demonstrated. Its value rests on an increase in the circulation through the extremities, as demonstrated by determinations of cutaneous temperature. Brown and his coworkers have shown that the temperature of the skin increases to a far greater degree than the temperature of the mouth when fever is artificially induced, and have expressed the belief that this excessive increase in temperature is due to vasodilation. A vaccine consisting of *Eberthella typhi* (*Bacillus typhosus*), *Salmonella paratyphi* (*Bacillus paratyphosus A*), and *Salmonella schottmülleri* (*Bacillus paratyphosus B*), injected intravenously, serves admirably for the production of fever. Pain is also alleviated. There are four disadvantages in the use of this vaccine: (1) the occurrence of a chill, (2) the absence of the desirable part of the reaction after repeated injections, (3) certain untoward effects, and (4) the comparatively short duration of the fever. The effect of the typhoid "h" antigen (Eli Lilly and Company) was studied by Barker, who found that, following 314 injections given to sixty-three patients, chill occurred in only 27 per cent. Malaise was less marked. The use of this antigen marked a distinct advance in protein therapy, for chill is assumed to be conducive to vascular thrombosis,[7] and is not useful in the treatment of peripheral vascular disease. The untoward complications following intravenous injections of typhoid and paratyphoid vaccine have been emphasized by Hench[7]. In a study of 10,000 injections in 2,500 cases he found unusual clinical phenomena subsequent to twenty injections in fourteen cases. Death occurred in three cases, a mortality of 0.12 per cent.

The history of the use of sulphur by injection has been reviewed recently by Mackay[8]. Subcutaneous injections were used by various investigators in 1907[2,4,5]; these authors believed it lowered the temperature in bronchopneumonia and pulmonary tuberculosis. Intramuscular injections of sulphur in oil were first used by Schroeder[12] in 1927 in the treatment of paresis. The literature regarding its use as a pyrogenetic agent in syphilis, in other conditions of the nervous system and in

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rheumatic disease has since increased considerably[4,6,9-13,15-18].

Our attention was directed by Mackay[8] to the use of sulphur in producing artificial fever. The first injection was followed by such satisfactory results (the healing of chronic ulcers of the toe in a case of thromboangiitis obliterans) that further investigation was carried out. We hoped it would have the following advantages: (1) safety of use for persons of advanced age, (2) production of prolonged fever, and (3) absence of disagreeable sequelae following injection. The first two desiderata have been realized. Schroeder[14] wrote that intramuscular injections of sulphur are without danger to infants, or to senile persons. Our series is small, but complications have not been noted in persons ranging in age from thirty-five to sixty-five years. Fever is present for a prolonged period as compared with that following injection of typhoid vaccine. In our experience, pain at the site of injection constitutes the single contraindication to the use of sulphur by the intramuscular route.

Technic and Dosage

A 2 per cent suspension of sulphur in olive oil* is injected deeply into the lateral aspect of the middle portion of the thigh. Warming and shaking of the suspension distributes the sulphur more evenly in the olive oil. Injections can be given every four or five days, using alternate thighs, and increasing the amount at each injection. The amount of the first injection is 1 c.c. Schroeder[14] increased each succeeding dose by 1 c.c. of 1 per cent suspension of sulphur in oil, giving as much as 10 c.c. at a single injection, and a course usually of ten injections. The greatest single dose we have used was 3.5 c.c. of a mixture of sulphur, 2 per cent, and olive oil. In our experience amounts in excess of 2 c.c. of the 2 per cent suspension have little, if any, advantage over the smaller amount and cause greater pain and more marked chill. Repeated injections of amounts of 2 c.c. have always been followed by satisfactory febrile response. Apparently, in paresis, results of treatment are dependent somewhat on the height of the temperature achieved. In persons with peripheral vascular disease, increases in the temperature of the skin are usually as great when the general body temperature is 1.5° to 2°C. above normal as with greater increases. We have never given more than six injections in sixty days to one patient. Typhoid vaccine was given intravenously between injections of sulphur.

*Supplied by the Abbott Laboratories, Chicago.

Material Studied and Effects of Sulphur Injected Intramuscularly

The present study deals with fifteen patients who received thirty-two injections of sulphur. The group includes ten patients with thromboangiitis obliterans, three with arteriosclerotic occlusive disease of the extremities, one with painful paresthesia, and one with sclerodactylia. In five additional cases, in which patients received twelve injections, detailed observations were not made. The ages of the patients varied from thirty to sixty-five years.

Fever began on an average of seven and six-tenths hours after injection. The greatest afebrile period following injection was thirteen and five-tenths hours; the shortest, seven hours (tabulation). Small doses of the suspension of sulphur tended to produce gradual increase in the temperature of the body; following larger amounts, the increase in temperature was more rapid. The average maximal temperature, following all injections, was 102.4°F. It is interesting that relationship is lacking between the amount injected and the maximal temperature attained. Five injections of 1 c.c. each produced an average maximal temperature of 102.1°F., and the temperature, after fourteen injections of 2 c.c. each, was only 0.3°F. greater, an increase of no appreciable value. The average duration of the fever following all injections was fifty hours (figure 1). Dosage had direct influence on the duration of the fever, which averaged only twenty-seven hours following injections of 1 c.c., and fifty-four hours following injections of 2 c.c. Larger amounts of sulphur produced fever of even shorter duration. Increase in the cutaneous temperature of the extremities occurred in a manner similar to that ob-

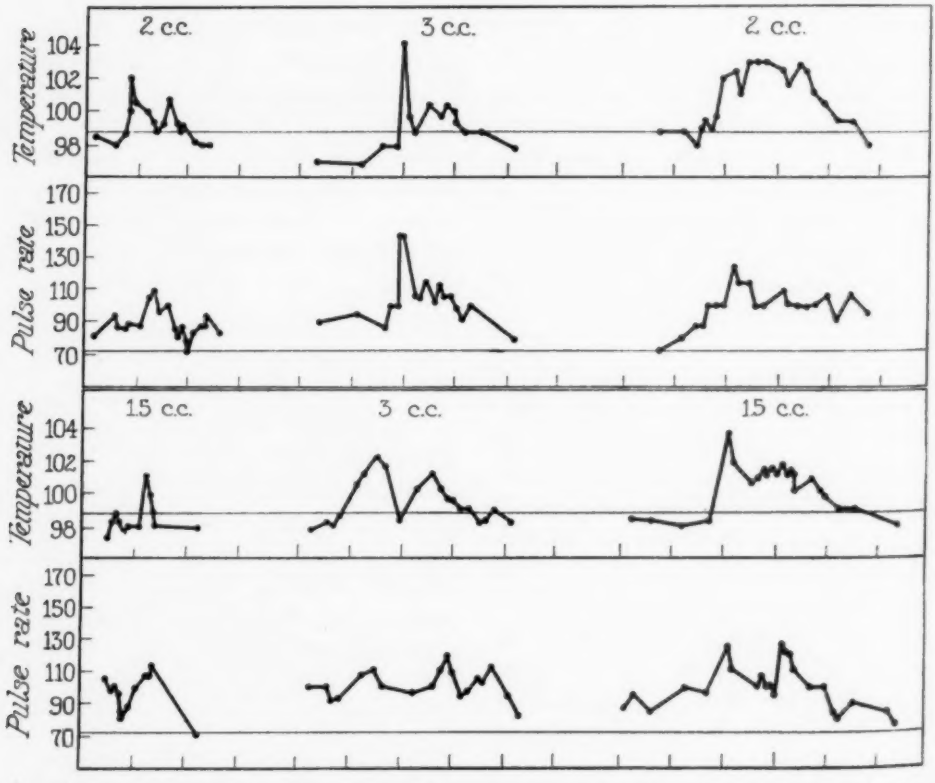

FIG. 1. Variations in the response of temperature and pulse rate to intramuscular injection of sulphur. The units laid off on the abscissa represent time in days.

served following intravenous injection of typhoid vaccine (figure 2).

Pain at the site of injection is the most disagreeable feature and the greatest objection to intramuscular injection of sulphur. Some patients complain little and others bitterly, but few wish the injection repeated, although none refused. In this regard, sulphur is far inferior to vaccine injected intravenously, for patients are unanimous in their preference to the discomfort caused by the vaccine as compared to that produced by sulphur. The distress may be divided into continuous pain, and that which occurs only with movement of the extremity. The pain begins from one to three hours after the injection, and continues on an average of twenty-six hours before there is spontaneous relief. During an additional average period of fifty-one hours pain is present on moving the extremity, but absent when the leg is at rest (tabulation). This period occasions little complaint. The larger amounts of sulphur produced longer periods of pain.

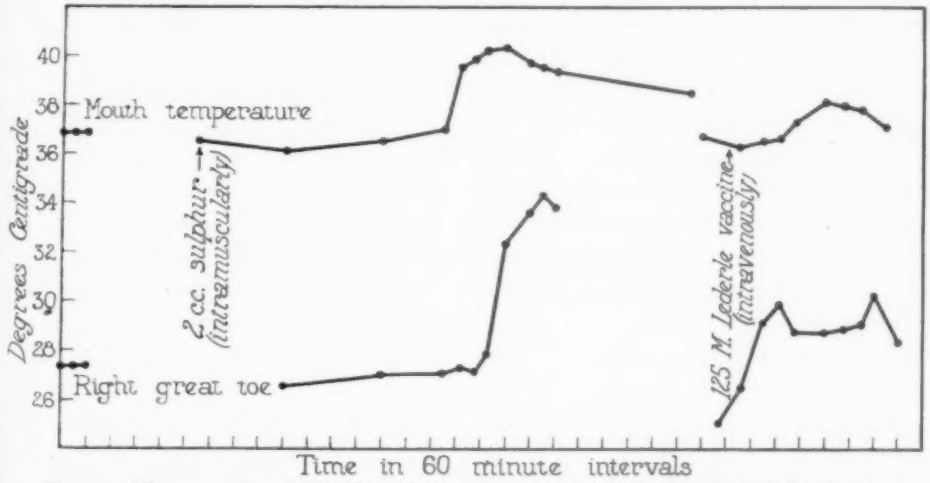

FIG. 2. The response of the dermal temperature of the same patient following intramuscular injection of sulphur in oil and intravenous injection of typhoid vaccine.

TABULATION

INTRAMUSCULAR INJECTION OF SULPHUR IN OLIVE OIL IN PERIPHERAL VASCULAR DISEASE

Amount injected, c.c.	Number of injections	Afebrile period, hours	Average duration of fever, hours	Average maximal temperature, °F.	Average time until onset of pain, hours	Average duration of severe local pain, hours	Average duration of all pain, hours
1.0	5	7.0	27.0	102.1	1.8	28	60
1.5	7	8.0	51.0	102.0	3.0	28	77
2.0	14	7.0	54.0	102.5	2.4	22	75
2.5	1	13.5	50.0	103.0	1.0	44	72
3.0	4	7.6	49.0	102.6	1.5	35	112
3.5	1	12.5	52.5	103.0	1.0	16	66

Our attempts to prevent the pain by injecting other materials with the sulphur and oil, although not extensive, were unsuccessful. A local anesthetic was tried on three occasions without benefit. As was expected, its effects had largely worn off before the pain had begun. The addition of 5 c.c. of the patient's blood to the injected sulphur and olive oil was likewise without beneficial effect. Prevention of the pain is highly desirable, and further attempts should be made. Mackay[8] has advanced experimental data as evidence that sulphur produced its pyrogenetic effect through local destruction of muscle, and it is possible that substances which may be found to prevent the pain will also eliminate the sharp, fever-producing effects of the sulphur. More intensive study of this phase of the subject is essential.

Thirteen of the fifteen patients had indolent ulcers associated with mild to very severe regional pain. In all cases, some degree of relief of pain was noted. After all injections of the suspension of sulphur in excess of 1 c.c., pain was only about half as severe as before. In one instance pain in the region of an ulcer disappeared entirely, but in general sulphur lacked some of the pain-relieving properties of vaccine injected intravenously. This study demonstrates that the fever and not the vaccine alone is responsible for the relief of pain with the patient at rest, in peripheral vascular disease. One patient with painful paresthesia of the feet did not receive relief from intramuscular injections of sulphur; later the pain was shown to be of central origin, for spinal anesthesia, with complete motor and sensory paralysis, likewise failed to give relief.

Chill occurred following seventeen of the thirty-two injections of suspension of sulphur. In ten of these instances the chill was graded 1 in severity; in four it was graded 2; in two it was graded 3, and in one it was grade 4. Twenty-six injections of suspensions in amounts of 2 c.c. or less were followed by chill in thirteen instances (50 per cent), but the chill was of minor degree (graded 1 or 2) in all but one instance. Patients generally complained but little of the chill and it was not a contraindication to the use of sulphur.

An increase in the number of leukocytes followed the injection of sulphur in all the cases studied. Frequently they numbered as many as 45,000 for each cubic millimeter of blood. Study of the blood smears revealed definite increase in the percentage of neutrophilic leukocytes. The number and percentage of the leukocytes in the blood reached normal values on an average of ninety-eight hours following injection of sulphur.

It is difficult to evaluate the effects on the ulcers of sulphur injected intramuscularly, for typhoid vaccine was given intravenously and local applications were also used in most of the cases. In two cases of thrombo-angiitis obliterans with gangrenous ulcers, in which courses of vaccine were administered, the condition of the ulcers improved after the first injection of sulphur and the lesions were healed in three weeks.

In five cases of thrombo-angiitis obliterans, with severe ulcers or gangrene, the course of the disease was

unmodified by treatment with vaccine and sulphur, and amputation was necessary. Five patients were spared amputation. In one case of arteriosclerosis of the extremities, amputation was later necessary. The condition of one patient improved sufficiently to allow successful amputation of a toe; that of one patient was unchanged during a short period of observation. The ulcers on the heels of one patient with sclerodactylia healed slowly under treatment with combined sulphur and vaccine. In general, the results of injections of sulphur on ulcers or gangrene, in patients with peripheral vascular disease, were equal to and occasionally exceeded the results following intravenous injections of vaccine. The temperature of the skin increased following injections of sulphur in much the same manner as it increased following intravenous injections of vaccine.

The Method of Action of Intramuscular Injections of Sulphur

Mackay has reviewed the opinions as to the mechanism by which sulphur injected intramuscularly produces fever. Impressed by the theoretic nature of these opinions he approached the problem experimentally. Rabbits were used, but even with doses, based on body weight, which exceeded by thirty times those used in man, fever was not produced. Sections taken from the region injected, twenty-four and forty-eight hours after injection, gave evidence of profound necrosis and marked inflammatory reaction; large numbers of polymorphonuclear leukocytes and a few lymphocytes were present. Less striation of the muscle fibers, with fragmentation and degeneration, was observed. Sections, taken thirteen days following injection, gave evidence of subsidence of the acute inflammatory process; there was evidence of proliferation of fibroblasts, and foreign-body giant cells and regenerating muscle fibers were seen. Olive oil was not essential to the production of the inflammatory reaction, for sulphur in a mixture of acacia, 1 per cent, in physiologic solution of sodium chloride produced the same pathologic changes as sulphur in olive oil. As a result of his experimental studies, Mackay expressed the belief that the fever which follows intramuscular injection of sulphur is a result of a reaction to protein liberated from the patient's own muscle, or that it is a result of the action of hydrogen sulphide formed from sulphur in the tissues. As Mackay logically pointed out, the afebrile period following injection, the increasing amounts of sulphur necessary, and the pathologic changes induced, argue for such a mechanism as was postulated by him.

Comment

The ideal pyrogenetic agent would be one which would produce fever of as long duration as is desired without disagreeable or harmful local or general reactions. Unfortunately such an agent is as yet unavailable. Intravenously injected vaccine, although a very valuable therapeutic aid, has the disadvantages that there is slight danger of complications, and that the fever is of comparatively short duration. Sulphur injected intramuscularly is superior to vaccine in that it can be used with safety for patients of advanced

age and in that the fever is of longer duration. It is inferior to vaccine because of its reaction and because of the distress occasioned at the site of the injection. The patient's attitude toward injection of sulphur varies: some patients request repeated injection because of favorable results; some extremely dislike, and nearly refuse, injection because of the pain induced.

Each patient should be informed of the pain before the injection is given; morphine or codeine should be used freely during the period of acute distress. Antipyretics, such as acetylsalicylic acid, should be avoided because of their effect in lowering temperature. As yet no permanent impairment of muscle function as a result of repeated injections has been reported even by Schroeder,[13,14] who has had extensive experience. On the basis of Mackay's experimental work, such changes in muscle function can be reasonably expected provided injections are repeated a sufficient number of times. For our purpose, in the treatment of peripheral vascular disease, a smaller number of injections than that which Schroeder gave without detrimental effects is usually sufficient. Increasing doses were not necessary for one patient who received six injections.

The evidence that sulphur itself is of therapeutic value in peripheral vascular disease is largely lacking in this study. Because of the pain at the site of injection, the use of intramuscular injections of sulphur in the future probably will be reserved for persons to whom the distress is not severe, for those who are temporarily insensitive to typhoid vaccine, and for those of advanced age. We cannot substantiate Mackay's observations that persons who do not respond well to vaccine do not respond to sulphur. Our experience is the opposite, and sulphur is commonly used when typhoid vaccine is ineffectual.

Summary and Conclusions

Observations were made on pain at the site of injection, on relief of pain in ulcerated or gangrenous regions, on healing of ulcers, on height and duration of fever, and on chill and leukocytosis in fifteen cases of peripheral vascular disease, in which thirty-two intramuscular injections of sulphur, 2 per cent, in olive oil were given. In five additional cases twelve injections were given, but detailed observations were not made.

Fever began about seven hours after the injection; the temperature reached an average maximal level of 102°F., and lasted an average of fifty hours. Chills occurred following approximately 50 per cent of the injections, but they were mild when doses of suspension of sulphur of 1.5 c.c., or 2 c.c., were given.

The most satisfactory dose in treatment of peripheral vascular disease was 1.5 c.c. or 2 c.c. Greater amounts were rarely necessary to produce effect even later in the course of the injections.

Clinical improvement was as marked following intramuscular injection of sulphur as that induced by intravenous injection of typhoid vaccine, and occasionally it was more striking.

The pain at the site of the injection varied from moderate to severe and constituted the greatest disadvantage

to intramuscular injection of sulphur in olive oil.

Sulphur in olive oil, injected intramuscularly, in the treatment of peripheral vascular disease, is most satisfactory for persons of advanced age, for those who are resistant to treatment by vaccine, and for those in whom the pain from the injection is not excessive.

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Mediastinal Displacement in Pneumothorax*†

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ROENTGENOLOGICAL study of pneumothoraces, whether artificially induced or spontaneous, frequently reveals mediastinal displacement. This displacement may be of the superior anterior mediastinum, of the inferior or of the entire mediastinum. The displacement associated with artificial pneumothorax therapy or in spontaneous cases is due to a disturbance of the normal physiological intrathoracic equilibrium. The degree of displacement is not in all cases proportionate to the change in intrathoracic equilibrium because of factors that will be discussed later.

Mediastinal displacement is observed in cases of pulmonary tuberculosis unassociated with pneumothorax and in cases where pneumothorax no longer exists; but this type of displacement will not be discussed in this paper.

The bulging or displacement of the superior anterior mediastinum is the type observed during fluoroscopic study of artificially induced pneumothorax cases. It is frequently noted during such study that the contralateral lung is encroached upon by the pneumothorax cavity bounded by the mediastinal pleura. This condition is ordinarily detected only during fluoroscopic study and is not observed on the routine x-ray plate. As stated by Sewell[1] the bulging only eventuates during the phase of expiration, and so far as it affects the respiration, it should operate to aid in the expiratory contraction of the lung and in the expulsion of its foul residual air. Contrawise, the inspiratory swing of the mediastinum toward the middle line allows, if it does not assist, the renewal of air of unusual oxygenation power to the full capacity of the contralateral lung.

Mediastinal displacement of the type influenced by the phases of respiration in artificial pneumothorax is usually in right sided pneumothorax, the mediastinal herniation or bulging invading the left chest. The reverse has been noted, but is a rather rare occurrence. When pneumothorax is induced on the left, the position of the esophagus obstructs mediastinal displacement from left to right. The displacement from right to left is possible because of an anatomical weakness between the two pleural cavities due to the fact that the aorta and superimposed esophagus lie somewhat to the

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left of the vertebral column. Displacement does not occur in most cases because the mediastinum is fixed, or practically fixed, by adhesions and thickening of the pleura. This condition is frequently the case in older adults and in long standing cases of pulmonary tuberculosis, and for this reason mediastinal displacements are most frequently observed in earlier cases of tuberculosis in younger adults where mediastinal mobility is not lessened by pleural thickening and adhesions.

Figure 1 illustrates the type of displacement under discussion, as shown on the x-ray plate. It is observed that the mediastinal pleura runs from the inner third of the clavicle downward to become continuous with the cardiac

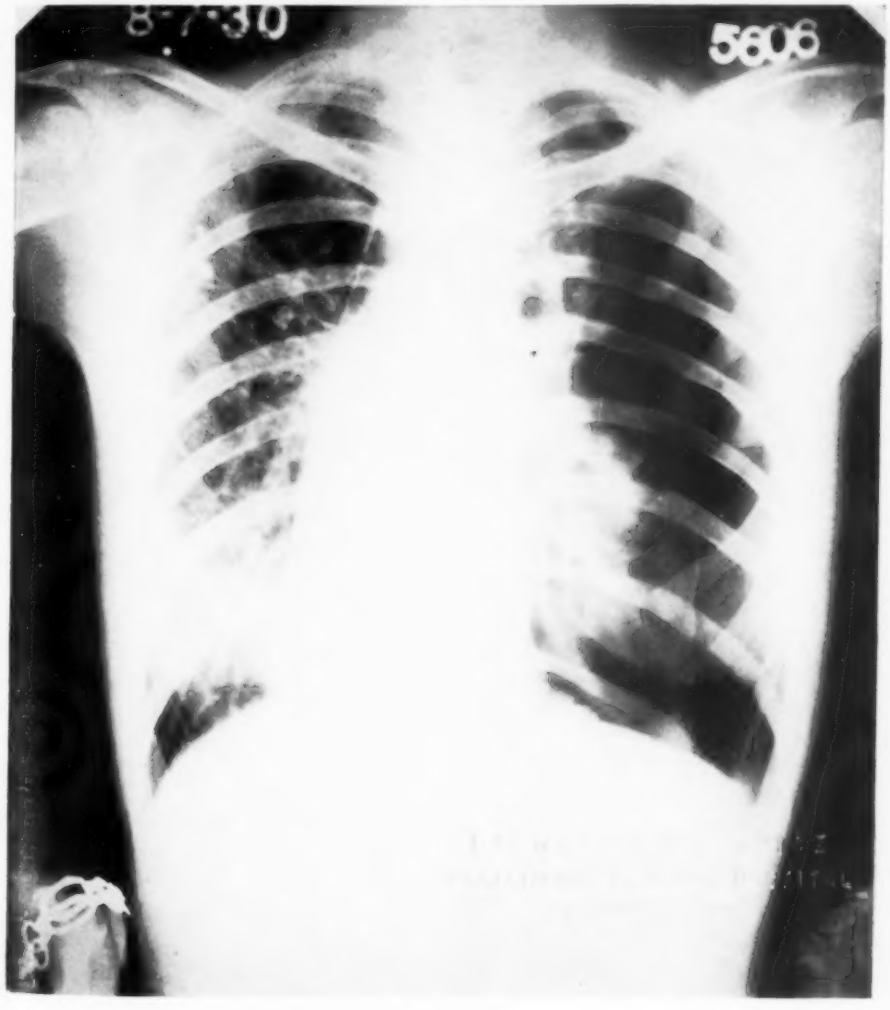

Fig. 1.

shadow at about the level of the third rib. As stated, routine x-ray plates seldom show the condition because they are usually made during the phase of inspiration, and during this phase the mediastinum moved toward the pneumothorax cavity. It is during fluoroscopy when the mediastinum can be observed, as to position, during inspiration and expiration that the apparent encroachment upon the contralateral lung is observed.

The condition is not a serious one and can hardly be classified as a complication. It is not associated with cardio-respiratory embarrassment. The encroachment as can be seen by lateral x-ray plates is not upon the lateral lung surface; but only upon its anterior surface. There is no lateral compression of the lung; but rather a slight anterior-posterior compression. The condition is of minor clinical significance and occurs in the presence of negative intrathoracic pressure.

Infrequently there is observed a superior anterior mediastinal displacement of an entirely different character. The right upper lobe of the lung herniates into the left chest, the hernial sac consisting of the mediastinal pleura. The hernia remains fixed in the left chest uninfluenced by respiration. There may be present respiratory embarrassment with a pressure sense to the stage of discomfort and the condition is considered of clinical significance. This condition is usually associated with positive pressure in the pneumothorax cavity of the right chest.

Figure 2 shows a hernia of the right upper lobe of the lung into the left chest. The plate is made during full inspiration yet the hernia encroaches upon the contralateral lung. Respiration produced no movement of the hernia. The mediastinum, except for the anatomically weak superior anterior mediastinum, was relatively fixed. The plate is of a patient who received a refill of gas in an eastern city prior to journeying to Denver, Colorado. The eastern city being near sea level and Denver being over five thousand feet in altitude, it is estimated that the intrathoracic pressure was increased approximately twenty per cent. The increase was sufficient to produce a moderately high positive intrathoracic pressure which was sufficient to push the firm fibrous right upper lobe into the anatomically weak area of the mediastinum. Ordinarily mediastinal bulging occurs in cases where the pleura is relatively free and elastic; but as pointed out by Dumarest and Brette[2] it may occur in cases with relatively nonelastic pleura when there is overstrong pressure in the pneumothorax cavity.

In this case the mediastinum must have been relatively nonelastic and fixed since the case is one of long standing pulmonary tuberculosis in an adult 42 years of age. Artificial pneumothorax had been used as an adjunct in his treatment for over one year. There were numerous band-like adhesions over the lower half of the lung, and at autopsy there was found one fibrous adhesion running from the visceral pleura to the mediastinal pleura.

In general, the degree of displacement depends upon flexibility of the mediastinum, the amount of intrathoracic pressure in the pneumothorax

space and the relative fixation of the mediastinal contents.

The factor of importance in this case was that of intrathoracic pressure. The removal of 800 c.c. of air from the right chest completely reduced the herniation of the lung with considerable reduction of the cardio-respiratory embarrassment. During fluoroscopy the mediastinal line could not be observed in the left chest, even during forced expiration.

Figure 3 shows the change produced by removal of air. The right upper lobe of the lung can now be seen in the right chest. The right lung has re-expanded somewhat, causing an elevation of the fluid level and the

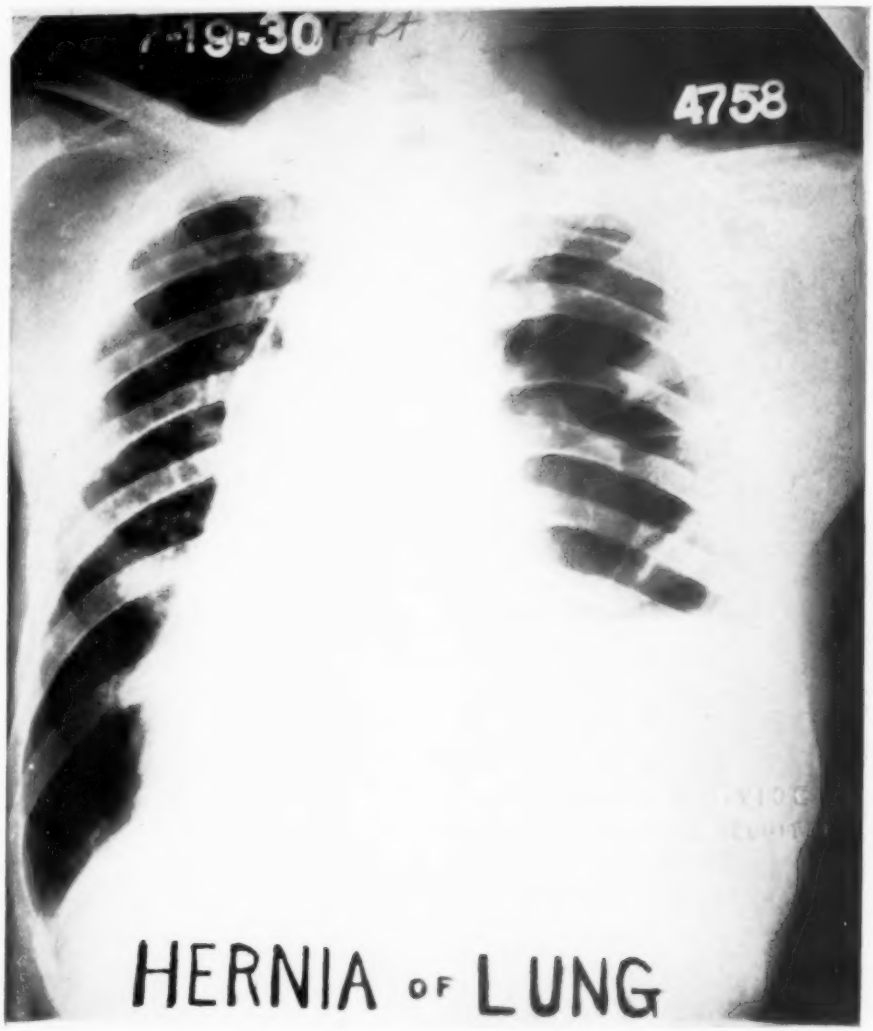

FIG. 2. Hernia of right upper lobe into the left chest.

mediastinal bulging into the left chest through the anterior superior mediastinum no longer exists.

We wish to emphasize the fact that such a condition is entirely different from the swinging superior mediastinum noted in young adults earlier in the employment of pneumothorax. In this case the mediastinal hernia contained a lobe of the lung from the opposite chest with a sufficient encroachment upon the contralateral lung to cause respiratory embarrassment. The hernia did not recede during inspiration and did not increase its encroachment during expiration;

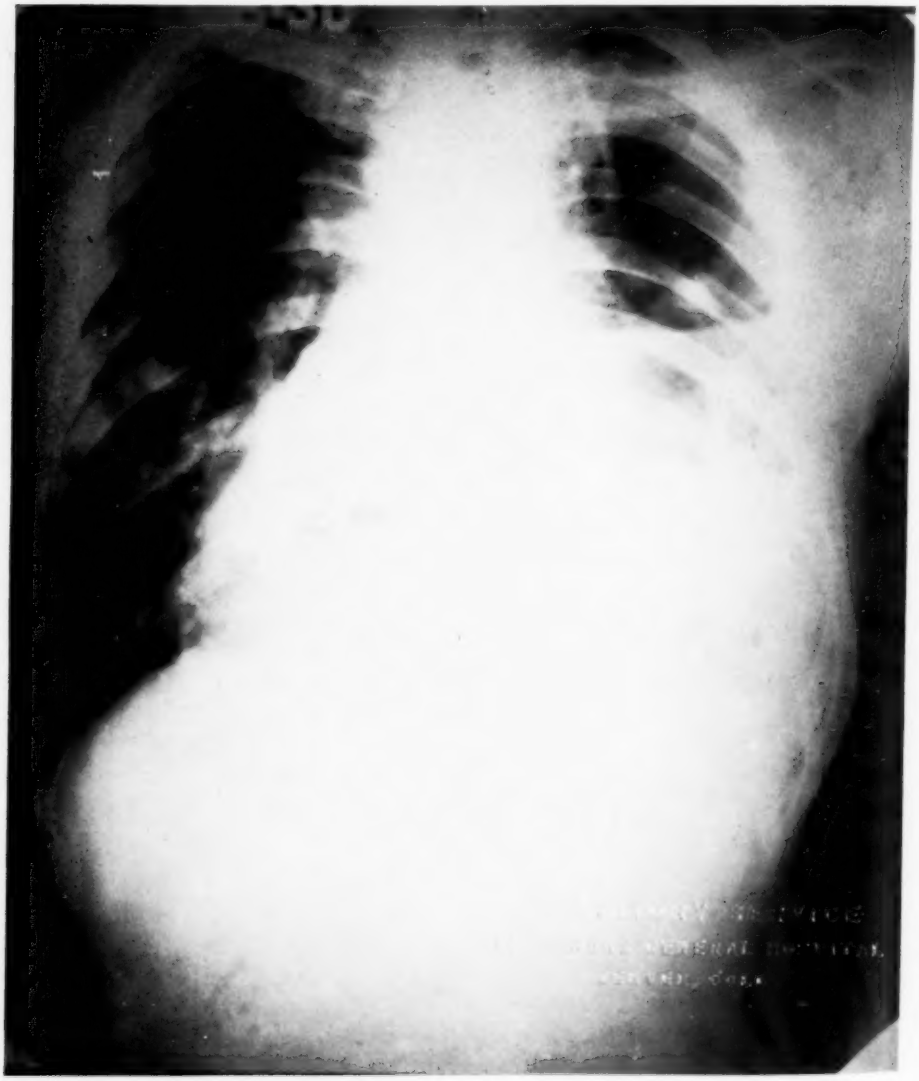

FIG. 3. Compare with preceding figure and note change produced by removal of air.

therefore it hindered oxygenation of the contralateral lung.

As stated by Stivelman, Hennell and Golembe[3] the size of the untreated hemithorax will be proportionately decreased and because of this its intrapleural pressure will be proportionately less negative. The intrathoracic pressure on the untreated side will be proportionately increased and will be equal to the intrathoracic pressure on the pneumothorax side minus the elastic recoil of the stretched mediastinum.

In our case under discussion the decrease in negative pressure of the untreated hemithorax was greater than usually observed because of the absence of an elastic recoil of the mediastinum.

A similar case is shown by figure 4. In this case there is also an actual hernia of the lung through the superior mediastinum. The plate is of a case of a closed spontaneous pneumothorax superimposed upon an artificial pneumothorax. Figure 4a shows the specimen removed at autopsy. The portion of the lung invading the opposite chest stands out as distinct protrusion from the rest of the lung.

In cases with a relatively mobile mediastinum there may exist a marked degree of displacement without aggravating cardiorespiratory embarrassment. In the absence of pleuroperi-

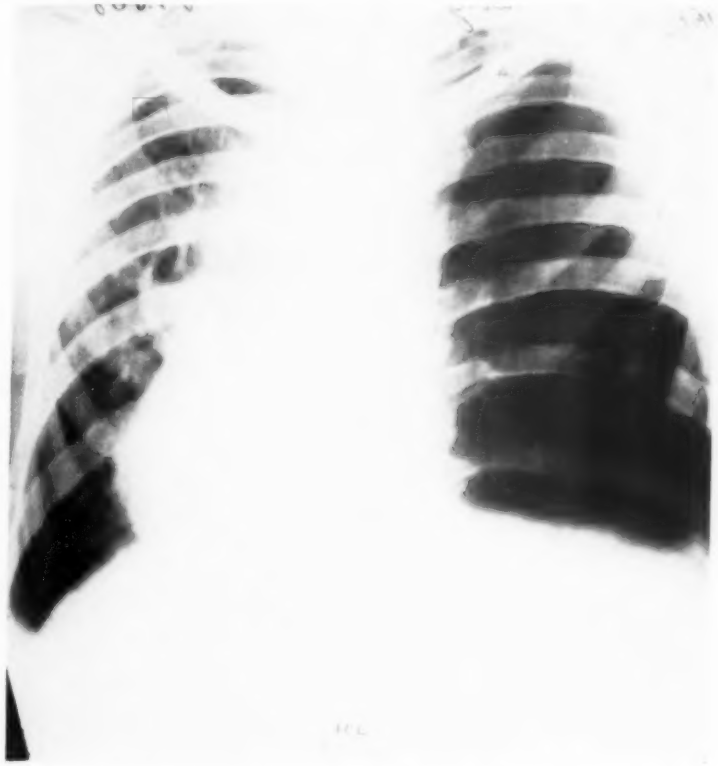

FIG. 4. Hernia of lung through the upper mediastinum.

cardial adhesions the heart may be converted into a complete dextrocardia without cardiac symptoms. We are now referring to the type of mediastinal displacement in which the entire mediastinum and its contents are pushed to one side. This condition is observed in spontaneous pneumothoraces with positive pressure, usually associated with pleural exudate. Whether or not there are acute symptoms depends somewhat upon the rapidity of the displacement. If the lung collapse is rapid in a case untreated by pneumothorax the symptoms are usually acute. Should the spontaneous pneumothorax be superimposed upon a previously existing artificially induced pneumothorax the symptoms may be extremely mild. In fact, the accident may happen and be unknown to the patient or his physician until it is detected by fluoroscopy prior to a contemplated pneumothorax refill. Apparently this type of displacement may occur to the right as well as to the left. However, the left to right displacement requires greater pressure and the degree of displacement is less.

Figures 5 and 6 show this type of displacement. These plates are of spontaneous pneumothoraces superim-

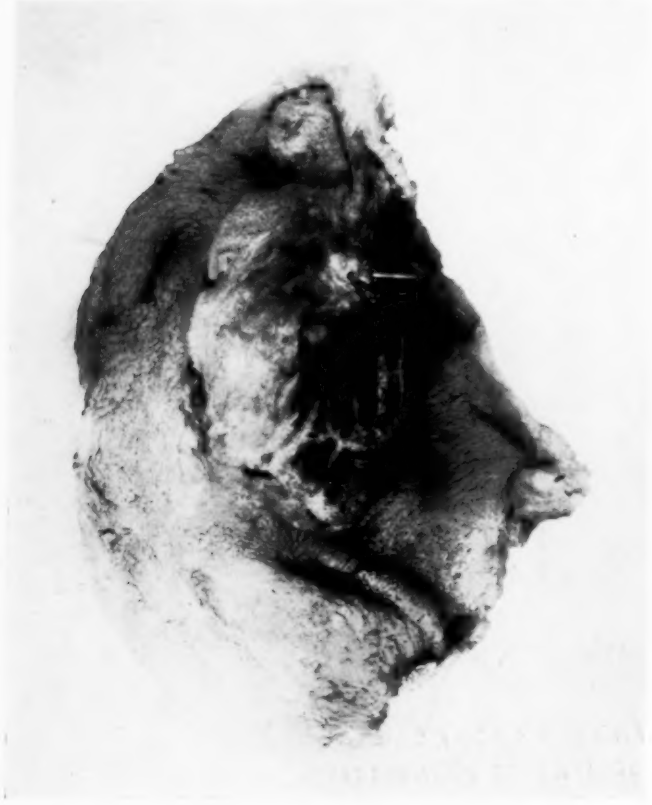

FIG. 4a. Gross specimen from case shown in figure 4. The protruding portion of the lung was the part which had invaded the opposite chest.

posed upon induced pneumothoraces, both showing pleural exudate. Both cases are of long standing and have few symptoms when the pleural exudate is removed at frequent intervals.

It has been noted in the earlier thoracenteses of such cases that the mediastinum returns to a practically normal position. Later in the treatment the mediastinum tends to become fixed in its displaced position and shows little tendency to return to its normal position after removal of pleural exudate. The same is true of the swinging movement of the mediastinum during respiration which also tends to become less and less and finally may become fixed. As the mediastinum becomes fixed in the opposite chest there then appears more respiratory embarrassment and sensation of pressure, relieved by removal of air with return of the mediastinum to nor-

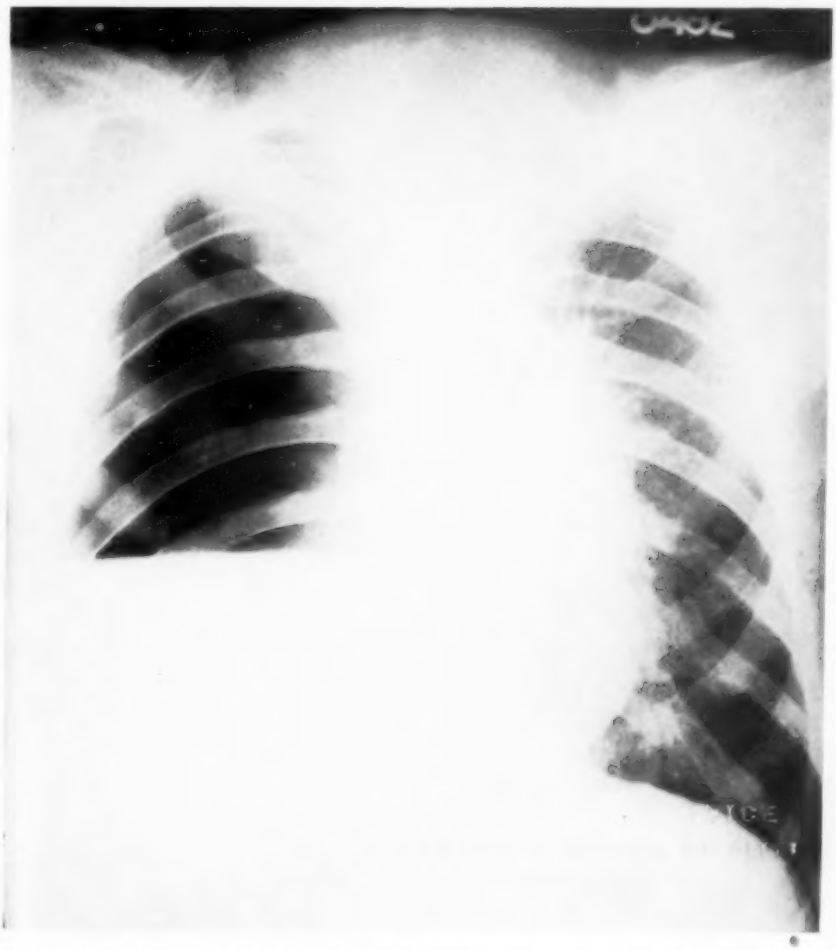

FIG. 5. Displacement produced by spontaneous pneumothorax superimposed upon induced pneumothorax, with pleural exudate.

mal position. In these two cases the lung remained collapsed because of a small bronchial fistula which existed for some time without infection of the pleural exudate. Bronchial fistulae were proven to exist by the introduction of dye into the chest cavity and noting same to appear in the sputum.

This type of case sooner or later becomes a surgical case because of the development of pyothorax. In some instances in which the fistula is small and tortuous and requires coughing attacks to force air from the respiratory tract to the pneumothorax space, there may be considerable interval before the pleural exudate becomes infected.

Another type of mediastinal displacement is the respiratory deviation of the entire mediastinum noted during fluoroscopy. This deviation, when

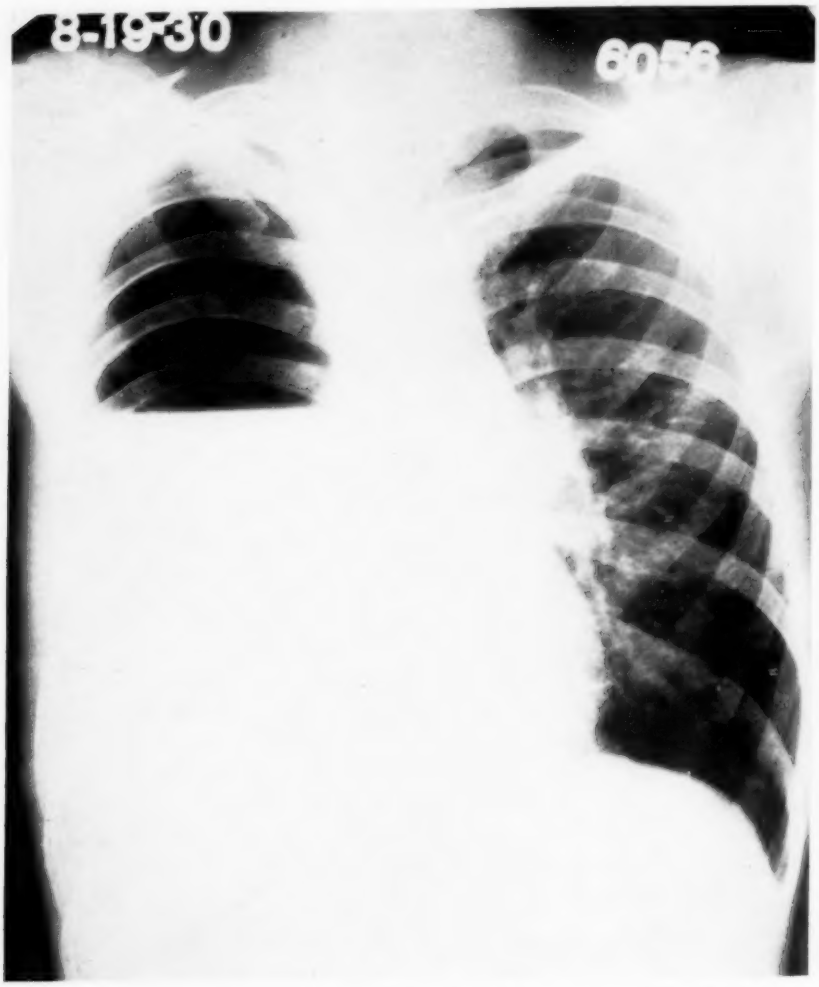

FIG. 6. Another example of the same type of displacement as shown by figure 5.

observed during forceful respiration, is rather astounding in some cases. It is believed that many who have not given particular attention to movements of the mediastinum would be rather surprised to note the degree of respiratory deviation in certain cases. The mediastinum in instances seems to encroach upon the contralateral lung to over one-half of its diameter. An observer may in haste conclude that this type of displacement is the factor of respiratory embarrassment. However, rather marked displacement is frequently seen in cases without symptoms. Let us again point out, as is shown by figures 7 and 8, the position of the mediastinum with reference to the phases of respiration. It will be noted that the mediastinum makes its encroachment upon the contralateral lung during the phase of expiration and recedes to the pneumothorax side on inspiration. Marked deviation is

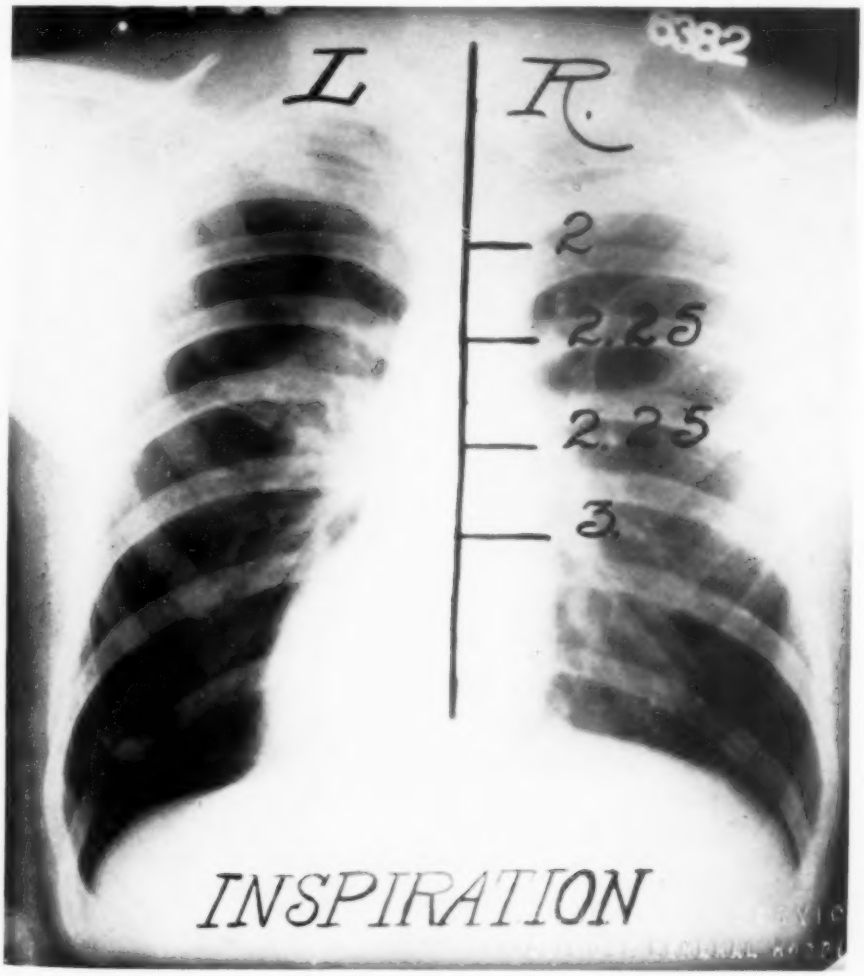

Fig. 7. Mediastinal relations during inspiration.

usually observed in younger adults earlier in the treatment by artificial pneumothorax. It has also been observed that as pneumothorax treatment is continued the mediastinal mobility tends to become less and less, finally becoming relatively fixed. This is due to the fact that the pleura becomes less elastic, and somewhat thickened under continuous pneumothorax treatment. Von Muralt[4] calls attention to the positive assistance given the respiratory function of the contralateral lung by the mediastinal deviation in therapeutic pneumothoraces. He also states that the situation here is the exact opposite to that found in wide open pneumothorax both as to mechanics and vital effects.

In cases of mediastinal deviation so well observed during respiration at the time of routine fluoroscopy there also exist characteristic manometer readings. The mediastinum is so flexible

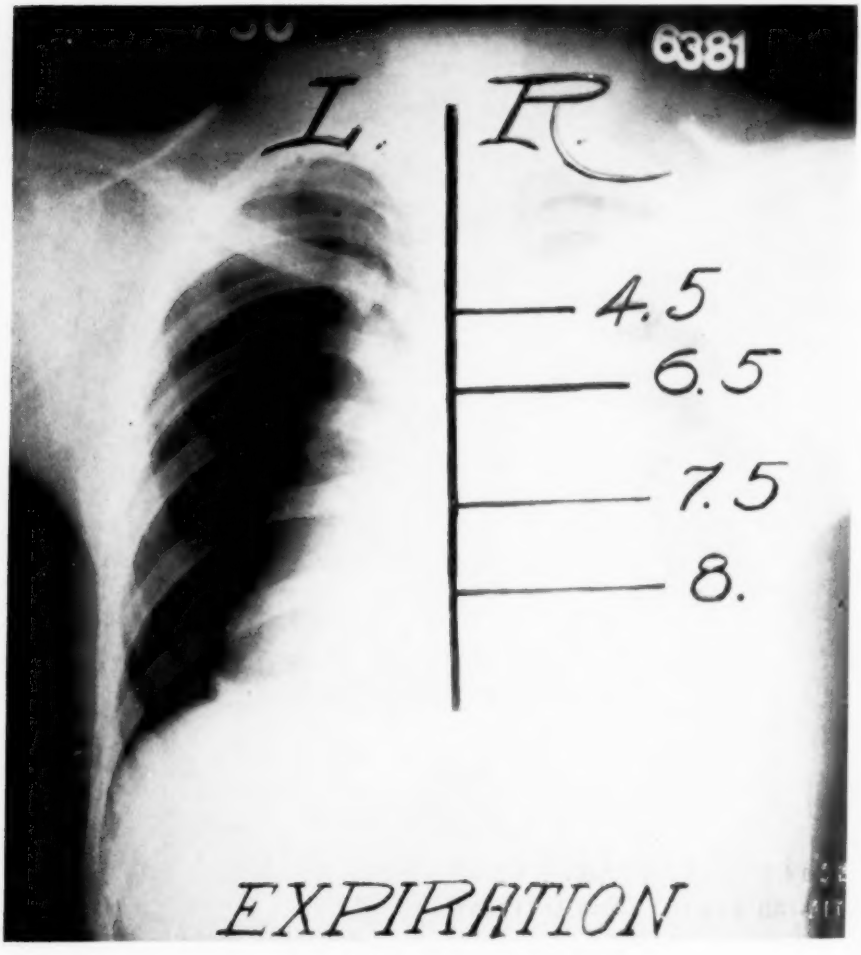

FIG. 8. Mediastinal relations during expiration.

that it is gradually displaced by the introduction of air into the pneumothorax cavity. This fact was discussed by Parfitt[5]. According to Boyle's Law, "The temperature remaining the same, the volume of a given quantity of gas is inversely as the pressure which it bears." This would mean that with rigid pneumothorax cavity walls there should be a proportionate change in the manometer reading following the introduction of each 100 c.c. of gas. It is not unusual, however, to observe that the manometer reading may show little change during the introduction of the first several 100 c.c. of gas. The interpretation of this is that the introduction of gas does not proportionately increase the pressure because the pneumothorax cavity has enlarged by mediastinal displacement.

Dumarest and Brette[2] state that disturbance of the mediastinum and the delicate organs it encloses causes functional trouble, such as dyspnea on exertion, and tachycardia uncomfortable for the patient, and may lead to a dislocation of the mediastinal partition without pulmonary compression being either complete or effective.

We know that rather marked deviation may occur without symptoms. There must be other factors than the displacement in itself which result in functional trouble.

With an elastic mediastinum, free of adhesions, in the young adult, where the pressure in the pneumothorax cavity is maintained well on the negative side there are usually no symptoms resulting from mediastinal deviation.

The most pronounced symptoms have been observed in left pneumothorax with pleuro-pericardial adhesions, and in longer standing cases with thickened pleura where pressure is employed to stretch adhesions for better collapse of cavitations. It has been our experience that functional symptoms are more apparent where pressure is applied to a relatively fixed mediastinum than where there is considerable deviation of a flexible mediastinum under negative pressure.

The movements of the mediastinum are called, by Stivelman, Hennell and Golembe[3] "Movements of Balance". They state that the intrathoracic pressure is established in pneumothorax as under all normal conditions. The change in pressure in one hemithorax must be balanced by approximate changes on the opposite side; and it is in response to this fundamental principle that certain so-called "Movements of Balance" take place in the chest cavity in pneumothorax.

When both hemithoraces are exactly alike in capacity and both lungs are equally expanded to fill them, there would be comparatively little or no disturbance in the relative position of the mediastinum during inspiration. On the other hand, supposing one hemithorax to be relatively immobile and the other hemithorax capable of large expansion, we can easily see how, during inspiration, a movable mediastinum would be shifted toward the large hemithorax because of the rapidly increasing negative pressure developed therein. It is believed that some understanding of the so-called "Movement of Balance" in pneumothorax is essential. The physics of

the phenomenon may upon superficial consideration appear rather confusing, but when one fully appreciates that we are dealing with differences in pressure and that the pressure changes with the phases of respiration, the movements noted under the fluoroscope are then understood. In fact, the phenomenon becomes simple. Appreciation of such movements leads to a clearer understanding of Kienboeck's phenomenon and other forms of paradoxical breathing.

We have been unable to demonstrate true paradoxical diaphragmatic breathing in artificially induced pneumothorax. The diaphragm has been noted to be lower than normal, may appear irregular in passing from the phase of expiration to inspiration and may appear to present a paradoxical movement of slight amplitude when the intrathoracic pressure on the pneumothorax side reaches a positive pressure at expiration. The apparent paradoxical movement disappears when the pressure is decreased or when position of the patient is changed toward the pneumothorax side.

True paradoxical diaphragmatic breathing is observed in pneumothorax cases when there is a paralysis of the diaphragm.

With the principle of "Movements of Balance" in mind an attempt was made to determine the approximate degree of incapacity of respiratory movement of the hemithorax required to produce movements of balance. Immobilization of the hemithorax by fixation of chest wall in a normal individual caused no "Movement of Balance". Fixation of the chest wall is partially compensated for by increased movement of the diaphragm. To prevent compensatory diaphragmatic breathing on the side of fixation, an individual was selected who had a paralyzed diaphragm due to phrenic exeresis. The individual selected showed a movement of the mediastinum during forced respiration. The right chest was immobilized, and x-ray made during full inspiration and another during full expiration, with the result that the mediastinum was found to remain practically stationary. The cardiac shadow was found to move through a distance of only nine-tenths of a centimeter.

It was found that procedures as outlined above were insufficient to produce mediastinal movements as frequently observed in artificial pneumothorax cases where lung compression ranges from twenty-five to fifty per cent.

Summary

A disturbance of the normal physiological intrathoracic pressure during the course of artificial pneumothorax therapy may produce mediastinal displacement when the mediastinum is sufficiently flexible.

Mediastinal displacements eventrating into the contralateral lung during the phase of expiration are of no clinical significance. However, fixed displacements in the presence of a relatively nonelastic mediastinal pleura produced by over strong pressure in the pneumothorax cavity may give rise to respiratory embarrassment and a sense of pressure to the stage of discomfort. A reduction of the displacement results in comfort to the patient.

Mediastinal displacement depends

upon flexibility of the mediastinum, the intrathoracic pressure in the pneumothorax cavity, and the relative fixation of the mediastinal contents.

A relatively flexible mediastinum usually occurs in younger adults early in artificial pneumothorax treatment, and the mediastinum tends to become less and less flexible as pneumothorax therapy is continued.

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Treatment of Recurrent Erysipelas*

By Harold L. Amoss, M.D., F.A.C.P., *Durham, N. C.*

RECRUDESCENCES and relapses are not uncommon in streptococcal infections. In facial erysipelas, the lesion may subside and the skin become almost normal but suddenly within a few hours all the signs and symptoms may return. When this occurs in facial erysipelas we have learned to suspect the presence of sinusitis. An example will illustrate this type of recrudescence:

Italian girl, aged sixteen years, admitted on the sixth day of an erysipelas infection involving both sides of the face, marked cervical adenitis and pharyngitis with obstruction to breathing. There was tenderness over both maxillary sinuses.

The symptoms of toxemia disappeared quickly after the administration of erysipelas antitoxin and the lesion began to recede but the fever did not abate for three days and then endured to a mild degree. Ten days later, both maxillary sinuses were irrigated and from the pus there was obtained a pure culture of beta hemolytic streptococci. The temperature came to normal and later rose, presaging severe serum sickness. Suddenly on the twenty-seventh day after onset, the patient complained of chilly sensations and headache and the temperature rose to 104°F. There was a rapid return of the lesion confined strictly to the areas previously involved but the skin was less shiny. The leukocyte count rose rapidly from 8000 to 15,000. The tonsillar and cervical glands were not markedly enlarged or tender. The nasal passages were completely stopped by dried mucosanguineous discharges. After shrinking and the removal of a large amount of bloody pus by suction, the patient felt much improved; the temperature fell sharply to normal within four hours, and within eight hours the erythema and swelling of the face had disappeared. The leukocyte count became normal in twenty-four hours Eighteen hours later the succession of events was repeated exactly, and the patient was discharged well, eight days later and has remained so for one year.

In other cases, treated with serum the skin previously involved and showing almost complete return to normal may become red, tender and swollen but not thick and brawny. Because of general glandular enlargement, arthritis and urticaria in other parts of the body and the failure in every case to cultivate streptococci from the skin, and also the subsidence of the lesion and the general signs, we regard this apparent recrudescence as a manifestation of serum sickness.

There is still another type of true recurring erysipelas in which the typical signs and symptoms recur after several months or years. Usually the succeeding attacks are milder than the first but recurring erysipelas may be severe and attacks vary in intensity. We have studied 25 such cases in the Danville State Hospital for the Insane. In eight of these patients there was no reaction to the endermal injection of 0.1 c.c. of a fil-

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trate of the broth culture of the erysipelas hemolytic streptococci. Of the remaining 17, three died of other causes during the year of observation. There remained 14 patients who had experienced from 2 to 5 attacks of erysipelas during the preceding two years and who, at the beginning of the study, reacted to one or more of the test strains. Without varying any other factor these 14 patients were given subcutaneously increasing doses of the streptococcus filtrate and tested for sensitivity every six months for two years. Ten patients reacted to both allergins. Further immunization with the second allergin reduced the sensitivity in all but three of them. Thus three patients remained sensitive and of these, two had a mild recurrent attack of erysipelas during the two years of observation.

In summary: 14 patients had 35 attacks of erysipelas in the two years before the immunizing experiment but among the eleven patients surviving the two years of observation and immunization there occurred only two attacks of erysipelas. Apparently the injection of streptallergin in these patients had a decided effect on the number and intensity of the recurring attacks.

The main purpose of this paper is to describe our experiences in a third type of so called recurrent erysipelas of the leg. These cases really belong to the category of cellulitis. As a preface to a description of chronic recurring cases there will be presented an acute case which initiated the reasoning approaching the allergic concept.

Case 1. Italian, male, 28, toes crushed. With dressings, the superficial lacerations healed in six weeks and the patient was ambulant for ten days. Suddenly, four days before coming to us, the dorsum of the foot became swollen, hot and painful, and with a high fever, the patient experienced chills, nausea and anorexia. He was admitted to the ward with cellulitis of the foot and leg, femoral and inguinal adenitis. The symptoms had increased. He was given intravenously and intramuscularly erysipelas antiserum. Within ten hours, the temperature was normal and the lesion began to recede so that within three days it had entirely subsided. Beta hemolytic streptococci were obtained in pure culture from a fluctuant tumor on the under surface of the second toe and from the skin lesion on the leg. The abscess on his foot healed slowly and the patient was discharged six and a half weeks after admission, as well. Four days later he noticed a slight and offensive discharge from about his toes on both feet but there were no constitutional symptoms. He walked without discomfort and seemed well for one month when he lost his appetite and felt unable to work. Four days later, he had suddenly a chill and within a few hours, the swelling, redness and pain appeared in the area previously involved. He was readmitted with a temperature of 103.6°, W.B.C. 19,000, and presented a picture practically identical to that of the previous admission, except that the skin over the involved area was a darker red. Cultures at this time were positive from the recurring abscess under the second toe but skin cultures from the involved area were *negative*. The abscess was drained and temperature became normal and the redness, swelling and tenderness of the skin of the leg disappeared completely. The patient has remained well.

At that time, it did not occur to us to compare the reactivity of the skin over the involved area to injections of toxic filtrates. But as the uninvolved skin was very reactive, he was used to test several fractions so that he received fourteen endodermal injections. When tested two months after discharge, the skin of the involved area was *less* re-

active than uninvolved areas. This is in accord with subsequent experience in a number of cases.

In the chronic recurring cases the lesion usually involves the lower leg which becomes swollen tender and intensely red. The skin usually remains thin and blanches on pressure but here and there are outcroppings of a true erysipelatous aspect in which the skin itself is brawny, is not blanched by pressure and blebs form. The dorsum of the foot may or not be involved but often the entire foot may be swollen. There is usually femoral adenitis and general symptoms such as fever, chills, tachycardia, anorexia and headache. The recurrences which may appear after an interval of two weeks or six months are usually ushered in by the general symptoms of which the first sign may be fatiguability or sudden chill. The patients recognize immediately by these symptoms that another recurrence is imminent. They remain in bed for five days to two weeks and seem perfectly well between the attacks.

The following case history in abstract will illustrate this type of infection:—

H. R. W., white man, aged 39 years, admitted September 24, 1927. Except for frequent colds up to four years ago when the sinuses were drained and tonsils enucleated, the patient enjoyed excellent health.

September, 1926, he suddenly experienced a chill and high fever. His left leg became reddened, swollen and quite painful from the ankle to a line 7 cm. below the knee. A diagnosis of osteomyelitis was made, but the tibia at operation was found to be quite normal. This attack endured about two weeks. He recovered the use of the leg completely but in January, 1927, (four months later) he had a similar affection of the same leg which lasted another two weeks. Since then there have been four more recurrences as follows:

Second attack: January, 1927, two weeks duration.

Third attack: April, 1927, eight days duration; right leg also involved.

Fourth attack: June, 1927, two weeks duration.

Fifth attack: July, 1927, three days duration.

Sixth attack: August, 1927, two weeks duration.

He felt well between attacks and in spite of five attacks in eight months gained 15 pounds in weight.

September, 1927. The general physical examination revealed nothing abnormal. Laboratory tests added nothing of interest. Cultures of the nose and throat failed to demonstrate streptococci or any other predominating organisms.

Between the toes on both feet, however, an epidermophyton infection was discovered, identified microscopically but not cultivated.

To determine sensitivity to several of the streptococcus filtrates, he was tested on September 29, 1927, by endodermal injections of C strain and B strain filtrates both on the leg and on the arm. He was found positive to both: the reactions were more marked on the legs. On October 5, immunization was started by gradually increasing doses of B filtrate subcutaneously. He was tested again to the toxic filtrate on November 26 (one and a half months later) when it was found that he did not react to B filtrate (used in his immunization) but still remained markedly positive to C filtrate. The reaction was more marked on the arm than in the area of the leg which had been affected. The patient has gained 8 pounds and feels well. He has applied salicylic dusting powder to the toes after washing them in warm water and alcohol, at least twice daily. The itching of the legs which previously had been severe enough to keep him awake, has disappeared.

Skin tests with 1 to 100 dilution of filtrates from two strains of erysipelas streptococci resulted as follows:

The control consisted of 0.1c.c. of 1 to 100 tryptic broth.

Date	Area tested	Filtrate	Reaction	Control
Sept. 29	left arm	Filtrate B	++	0
		Filtrate C	++	
	left leg	Filtrate B	+	
		Filtrate C	++	

Subcutaneous injection of increasing doses of B filtrate were made at five-day intervals from October 10 to November 21.

Date	Area tested	Filtrate	Reaction	Control
Nov. 26	left arm	Filtrate B	±	0
		Filtrate C	+++	
	left leg	Filtrate B	0	
		Filtrate C	+	

From November 26 to February 5, at five day intervals increasing doses of C filtrate were injected subcutaneously. Tests were made again on May 19, 1928. The skin of the arm and leg reacted to filtrate of strain C but not to filtrate B. The reactions were more intense on the arm than on the leg.

This patient has had no recurrence in 3 1/2 years.

Two points in this abstract form the basis of our present method of treating such patients.

1) The skin on the affected side when tested during the interval between attacks, reacted to a greater degree to the endermal injection of the streptococcus filtrate (so called streptallergin) than the skin of the other leg, or of the arm. A course of injections of gradually increasing doses of the streptallergin was followed by the state of nonreactivity earlier in the affected area than in the other leg. Because of this fact it may be assumed that the skin over the involved area was in a state of hypersensitivity. The involved area has not been more reactive in but 15 of the 23 cases tested, but in every patient there was a marked reaction. The tentative hypothesis that the lesion is an allergic response is supported also by the fact that in no instance has it been possible to cultivate hemolytic streptococci from skin puncture. It has been shown by biopsy that a few organisms are present (culture) yet they are sparsely scattered in small nests throughout the tissues.

2) The second point is the presence of a break in the skin between the toes on the affected side from which epidermophyta were seen in the scrapings. In some cases they have been cultivated. In every case there has been a fungus infection on one or both feet and when the lesion is visible on only one side it is invariably on the side on which the recurrent cellulitis appears.

In four cases hemolytic streptococci have been obtained from culture of the debris removed from the edge of the toe nails.

The plan of the treatment is as follows:—The skin at symmetrical points on the legs is tested for sensitivity by the injection of 0.1 c.c. of 1-100 filtrate from 6 stock strains. The strain provoking the greatest reaction is used as the desensitizing agent. Increasing doses of 1-100 dilution are given at five day intervals usually doubling the dose each time. The process is then continued with 1-10 and finally with the undiluted filtrate. After 5 doses of 1 c.c. of the undiluted filtrate the areas are gain tested and if the reaction zone measures over 1 cm. at 24 hours the injections are continued with

the filtrates which provoke reaction.

Inasmuch as it is probable that the fungus infections open the way for the entrance of the streptococci, efforts are directed toward the removal of this very resistant infection. The routine procedure is as follows:—

Whitfield's ointment, which is a 5 per cent salicylic acid salve is reinforced by the addition of 1 per cent thymol iodide and applied each night. After cleansing with soap and water the next morning the skin between the toes and of the soles of the feet is wiped from 70 per cent alcohol and a 1 per cent solution of thymol iodide in 70 per cent alcohol is applied and allowed to dry. A dusting powder of the following composition is used:

Salicylic acid	5.
Thymol iodide	1.
Boric acid	
Starch aa	50.

and when the socks are changed at 5 P.M. the affected areas are cleansed as in the morning. Soiled socks are boiled as soon as possible after removal.

Among the 23 patients treated (of whom 3 are still under observation) there have been no recurrences. The longest period of observation is 3½ years. In two other cases of recurring lymphangitis following burns with extensive scarring the treatment seems to be little value.

The 23 patients studied have come from the several states: two from New York, two from Texas, one from California and the remainder from the South Atlantic States.

It is possible that the immunizing process is not necessary. Perhaps the care of the feet is the essential point and it is recommended that this be tried first.

The Historical Development of the Present Conception of Cardiac Conditions in Exophthalmic Goiter*

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ALLOW your imagination to wander back five hundred years and picture a medieval castle upon a mountain top. Note how it stands majestically, a towering and commanding edifice. You might compare this castle to the thyroid gland, standing as it does at the top of human emotions and commanding its every act. It is then, and then only, that you are able to appreciate this small but "mighty" organ whose symptoms are expressed in practically every tissue in the body. The thyroid gland may be responsible for symptoms manifested in the skin, blood, bones, joints, muscles, the lymphatic glands, the nervous system, the gastrointestinal system, the genito-urinary system, the metabolic system, the endocrine system and, probably most conspicuously, in the cardiovascular system. It is, indeed, important to remember that these distant areas may first call the attention of the alert physician to pathology of the thyroid gland. All grades and variations of these referred symptoms are experienced and, I am sorry to say, it is not rare for even the mature doctor of note to miss the diagnosis. In other words, I desire to emphasize the fact that we must remember that, although thyrotoxicosis is a localized disease of the thyroid gland, it has myriads of generalized symptoms which may be manifested anywhere from the head to the toes.

These distant symptoms may precede for months any enlargement of the thyroid gland and it is not unusual to encounter cases which *never* show any thyroid enlargement whatsoever.

Fate is a trickster and often barely misses making an individual immortal. Such was the case with the Bath physician, Caleb Hillier Parry,[1] who described exophthalmic goiter, as we know it today, fifty years before either Graves or von Basedow discovered the symptom complex. Osler often said that Parry should be given credit for having first clearly described hyperthyroidism. Not only did he describe this disease but he was the first to call attention to the symptoms referable to the heart. This was in 1786. I shall quote his first case.

"There is one malady which I have in five cases seen coincident with what appeared to be enlargement of the heart, and which, so far as I know, has not been noticed, in that connection, by medical writers. The malady to which I allude is enlargement of the thyroid gland.

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"The first case of this coincidence which I witnessed was that of Grace B., a married woman, aged thirty-seven, in the month of August, 1786. Six years before this period she caught cold in lying-in, and for a month suffered under a very acute rheumatic fever; subsequently to which, she became subject to more or less of palpitation of the heart, very much augmented by bodily exercise and gradually increasing in force and frequency till my attendance, when it was so vehement, that each systole of the heart shook the whole thorax. Her pulse was 156 per minute, very full and hard, alike in both wrists, irregular as to strength, and intermitting, at least once in six beats. She had no cough, tendency to fainting, or blueness of the skin, but had twice or thrice been seized in the night with a sense of constriction and difficulty of breathing, which was attended with a spitting of a small quantity of blood. She described herself also as having frequent and violent stitches of pain about the lower part of the sternum.

"About three months after lying-in, while she was suckling her child, a lump of about the size of a walnut was perceived on the right side of her neck. This continued to enlarge till the period of my attendance, when it occupied both sides of her neck, so as to have reached an enormous size, projecting forwards before the margin of the lower jaw. The part swelled was the thyroid gland. The carotid arteries on each side were greatly distended; the eyes were protruded from their sockets, and the countenance exhibited an appearance of agitation and distress, especially on any muscular exertion, which I have rarely seen equalled. She suffered no pain in her head but was frequently affected with giddiness.

"For three weeks she had experienced a considerable degree of loss of appetite and thirst, and for a week had edematous swelling of her legs and thighs, attended with very deficient urine, which was highly colored, and deposited a sediment. Until the commencement of the anasarcous swellings, she had long suffered night sweats, which totally disappeared as the swellings occurred. She was frequently sick in the morning and often threw up fluid tinged with bile.

"She nursed for a year the child of her first lying-in, during which time she did not menstruate. Subsequently to that period she had five times miscarried; and for the last four months her menses had been irregular as to intervals and defective in quantity and colour. Bowels usually lax and more especially so for the last three weeks. It was directed that six ounces of blood be taken from her arm and that she should take twice a day, a pill consisting of dried Squill and quicksilver triturated with Manna, of each, one grain.

"The bleeding almost immediately relieved the dyspnea and stitches across the sternum. But the edematous swellings were increased and the urine did not exceed half a pint in twenty-four hours. She had been purged seven or eight times each day. Her pulse was 114, full and hard, and never more than six strokes without intermission. This was the state of symptoms on the sixteenth of August. The bleeding was ordered to be repeated and the pills to be continued.

"I did not again see her till the twenty-fifth when she had taken eight of the pills, which did not affect the mouth, but had produced seven or eight watery stools daily. The urine, however, did not amount to three ounces in the twenty-four hours and was very high colored and extremely turbid on standing, with a copious sediment. Her drink was about a quart in the day. Each systole of the heart shook the whole trunk of the body. The edema had extended itself nearly to the navel.

"The pills were repeated and she was ordered to drink freely of a solution of supertartrate of Potash. From this time no farther application was made to me respecting this patient who, probably, soon paid her debt to nature."

In 1802, Flajani[2] described heart disturbances in a disease characterized by a tumor in the anterior part of the neck. In 1828, Adelman[3] was the first to associate goiter with certain types of heart disease. It was he who coined the word: "Kropfherz". In 1835,

Graves[4] described the syndrome. In 1840, Von Basedow[5] called attention to the triad of goiter, cardiovascular symptoms and exophthalmus. In 1863, Potain[6] contributed a clinical discussion to the subject. The same year Trousseau[7] used tincture of iodine instead of tincture of digitalis by mistake on a toxic thyroid heart and, when he discovered his error and stopped the iodine, the heart condition was made worse. In 1878, Rose[8] first emphasized the importance of the heart in sudden deaths of patients with goiter. He felt it was due to a mechanical factor. In 1879, Lockridge[9] wrote about this disease and wished to name it "Cardiac Exophthalmic Goiter." Others, at this time, reported cases which they believed to be very much influenced by nervous factors. In 1896, Möbius[10] emphasized the importance of tachycardia, palpitation, forceful beating of the heart and the arrhythmia in these cases of thyroid disease and stated that exophthalmic patients "suffer and die through their hearts, practically always is the condition of the heart important." In 1899, Kraus[11] was the first to suggest the toxic theory of exophthalmic goiter. It was Kocher[12] who said that he believed the surgeon should be guided by the cardiac condition in choosing the time and the extent of the operation and that there were probably no cases of exophthalmic goiter in which cardiac symptoms were completely wanting.

As we come down to the present time, we find the pendulum is swinging to the opposite side. We hear authorities such as Willius, Boothby and Wilson[13,14] say that "the most outstanding fact is the infrequency in both exophthalmic goiter and adenoma with hyperthyroidism of symptoms indicating cardiac disease". Hurxthal[15] states that there is "no evidence that thyrotoxicosis injures normal healthy hearts because there is very little, if any, evidence of damage in cases under forty". Too, Lahey and Hamilton[16–19] write that "young individuals with previously undamaged hearts suffer no cardiac changes, no matter how intense the toxicity."

How are we to reconcile our clinical findings with these recent statements?

Let us for a moment turn to the pathological and experimental data at hand. Wilson[20] in eighteen cases of hyperthyroidism found that the myocardium showed "swollen fibers with indistinct striations and well-marked lipoid changes". Only five patients were under forty. He further states "that in patients with long-continued pronounced hyperthyroidism the myocardium shows more-advanced fat-changes than are present in the myocardium of individuals of the same age without hyperthyroidism."

Fahr[21] described two patients who died of heart failure following partial thyroidectomy. He found an interstitial myocarditis with an accumulation of round cells between the muscle fibers and in the neighborhood of small vessels, as well as degenerative changes, such as fragmentation and destruction of muscular fibers. He further described three other patients with hyperthyroidism who also showed, at autopsy, small round cell infiltration, fatty degeneration and hyaline focal necrosis.

Goodpasture[22] had two cases with auricular fibrillation who died of myocardial exhaustion. One showed a focal necrosis of the myocardium and the other an extensive necrosis. However, these two patients had pathology other than the hyperthyroidism which could account for the myocardial necrosis.

More recently, Thomas[23] reports a case of exophthalmic goiter with cardiac decompensation, who died on the third day. He found a slight increase in connective tissue about a few blood vessels, a slight infiltration of polynuclears and mononuclears between the strands of fibers. The cause of death of the patient, however, was a coronary thrombus. He reports an exophthalmic goiter patient with cardiac decompensation and auricular fibrillation of more than a year's duration, who made such a complete recovery that he felt that severe intoxication certainly need not produce permanent cardiac damage.

Hashimoto[24] examined two hearts from exophthalmic patients and found "lymphocytic infiltration between muscle fibers or around blood vessels".

These reported cases are too few to permit us to form a definite opinion.

Goodpasture[25] fed rabbits thyroid extract and thyroxin and found "slight but definite lesions in the myocardium, notably perivascular necrosis or fibrosis in the wall of the right ventricle, focal necrosis or fibrosis in the papillary muscles of the left ventricle and more rarely scattered small focal necrosis within the myocardium elsewhere". "With chloroform inhalation, these animals showed widespread myocardial necrosis." He, therefore, came to the conclusion that "hearts overstimulated by disease of the thyroid and laboring in a condition bordering on exhaustion were in a state of greater susceptibility to injury by toxic substances, such as may have resulted from a relatively mild terminal infection which, under other circumstances, might not have injured the myocardium". This conclusion is certainly well-worth remembering. Tonsillectomy or pulling of the teeth, in such a patient, may bring disastrous results.

Hashimoto[24] produced experimental myocarditis in animals with toxic doses of dried thyroid substances and found interstitial tissue lesions not unlike the Aschoff nodules in acute rheumatic fever and when the lymphocytic infiltration was increased it caused disintegration and destruction of muscle fibers. The hearts of these animals showed enlargement.

Farranti[26] found in the hearts of thyroid-fed cats and rabbits swollen muscle fibers with few nuclei and no transverse striations. Iscovesco[27] found that repeated injections of thyroid extract produced, in rabbits, hypertrophy of the heart. Other organs, such as suprarenals, ovaries, uterus, spleen and kidneys shared in this enlargement. Hoskins,[28] Herring,[29] Hewitt[30] and others[31] obtained similar results, namely: hypertrophy of the heart and hypertrophy of the other organs. Experiments by Simonds and Brandes[32] who fed dessicated thyroid to dogs resulted in further proof that there is an actual hypertrophy of the heart.

Certainly these experimental findings cannot be ignored.

Does the heart have more work in thyrotoxicosis? Davies, Meakins and

Sane[33] report an increased minute volume output of the heart in thyrotoxicosis and this increase is proportional to the increase in metabolism. The systolic output per beat of the heart decreases after thyroidectomy. Fullerton and Harrop[34] found a parallelism between the increase in basal metabolism and cardiac output per minute. Rabinowitch and Bazin[35] are the only ones who did not find an increased cardiac output in thyrotoxicosis. Robinson[36] studied a case of thyrotoxicosis and found that the cardiac output was actually increased to a greater degree than the oxygen consumption of the body. This means that, in this disease, there is a constant extra load imposed on the heart. In this particular case, Robinson found after thyroidectomy that the minute output fell from 10,000 c.c. to 3,890 c.c.; while the metabolism fell from plus 58 to plus one. This gives us some idea as to the great amount of work the heart does in thyrotoxicosis. Burwell and his coworkers[37] found a definite increase in cardiac output in thyrotoxicosis.

What are the subjective symptoms referable to the cardiovascular system in thyrotoxicosis? At the outset, let me state that there is little difference in the cardiac disturbances, between exophthalmic goiter and the adenoma with secondary hyperthyroidism. It must be remembered, however, that exophthalmic goiter is usually found in much younger individuals than is adenoma with hyperthyroidism. For that reason, we must expect physiologic changes in the cardiovascular tree in these older patients with adenoma and secondary hyperthyroidism.

Probably the first symptom of which these patients complain is palpitation or being conscious of their heart action, usually brought on by mental or physical exertion of a mild nature. The sensation of pounding in the chest will naturally unnerve an already highly-nervous patient. Sometimes, there are attacks of palpitation of a paroxysmal nature and it is then that we suspect an irregularity. Soon these patients notice undue breathlessness or fatigue on the least exertion. It is not long, thereafter, that this dyspnea becomes more marked. The patient flushes freely and spasmodically on account of the great lability of the vasomotor system. A common complaint is the throbbing in the neck and a sense of tightness or constriction of it. Quite often distress over the precordia or a fullness in the chest may send the patient hurriedly to the doctor. This distress or fullness, even called pain by some, is not severe. There is no radiation of this discomfort and usually it is designated as being in the region of the apex or toward the anterior axillary line.

Upon *inspection*, we see increased carotid pulsation and flushing of the face and neck. The skin of the face, neck and upper chest has a salmon hue, hyperemic and somewhat pigmented. The peripheral vessels, too, may show increased pulsation. Capillary pulsations are frequently noted. Looking at the precordia, we note a forceful apex impulse which gradually increases its power and, as time goes on, the apex beat becomes diffuse and can be noted moving downward and outward.

Palpation reveals a rapid pulse, soft and, at times, dicrotic; it might even be somewhat of a water-hammer pulse. Tachycardia is always present. The rate varies tremendously from day to day. Elliot[38] tersely puts it: "A patient showing a persistent tachycardia, temporary or permanent, should always be thought of at least, as a possible thyroid." Too, Gmelin[39] called attention to certain characteristics of the tachycardia; that it is constant with bed rest at night; that it is not influenced by drugs or narcotics; and that it disappears promptly after operation.

This increased rate is not evidence of heart disease but is evidence of a response to the increased demands made upon the heart by the increased metabolism. The precordia reveals to palpatation, a forceful apex beat, first localized and then diffuse and moving to the left and downward as the disease progresses. Quite often we are led to believe that we are feeling a systolic or even a presystolic thrill. At the pulmonic area, we may feel a distinct shock due to the violent closure of the pulmonic valve.

When the heart is *percussed*, we get a definite increase of the relative dullness downward and outward; later, the right border-dullness is increased. Ofttimes the base shows an increased dullness.

Auscultation reveals a whistling sound, a bruit over the carotids and their branches, particularly over the thyroid arteries. A so-called "pistol-shot" may be heard over the brachials and femorals. The sounds of the heart are loud, especially so is the first sound. Often two types of murmurs are heard; both are systolic in time and blowing in quality. One is best heard at the third left intercostal space and is localized. The second is best heard at the apex and has a variable transmission. It is thought that the first is probably due to changes in the blood-flow, while the apical murmur is probably due to functional regurgitation at the mitral valve due to dilatation of the left ventricle. Improvement or cure of the hyperthyroidism results in the disappearance of these. It must be remembered that in hyperthyroidism, we never hear diastolic murmurs unless there is an associated heart lesion and this, of course, might be present.

Willius and Boothby, in a series of toxic thyroid patients found, for exophthalmic goiter, a blood pressure average of 147 systolic and 73 diastolic and a pulse rate of 123, while in the adenoma with secondary hyperthyroidism, the systolic average was 153 and the diastolic was 83 and the pulse rate 110. It is seen that in the toxic adenoma patient, the systolic blood pressure is elevated considerably more than it is in exophthalmic goiter and it differs also from exophthalmic goiter in that the diastolic is also increased. "It is rare to find in exophthalmic goiter a diastolic over 90; while in toxic adenomas, it is not unusual to find readings over 100." Bed rest and activity, either physical or mental, will obviously influence blood pressure readings.

Harris[40] noted a relationship between pulse rate and pulse pressure in exophthalmic goiter. In tachycardia due to bacterial toxins, acting on the heart muscle; in the tachycardia of

other forms of myocardial disease; in the tachycardia of cardiac neurasthenia and in the tachycardia of heart failure, the pulse pressure is usually diminished and Harris believes that it is only in exopthalmic goiter that there is both an increase in pulse rate and, at the same time, a high pulse pressure. It is interesting to note that blood pressure readings in auricular fibrillation are the same as in normal rhythmic cardiac action.

It is an old fact now that in thyrotoxicosis, there is an increased basal metabolism. The resulting rapid pulse rate and heightened pulse pressure is a physiologic response to bring about an increased rate of circulation. Means and Aub[41] noted a close parallelism between pulse rate and metabolism in about sixty per cent of cases; while in the remainder, there was only a certain amount of parallelism. They concluded that, in exophthalmic goiter patients, just as Benedict and Murchhauser[42] concluded in normal cases, there is a relationship between heart rate and metabolism in different individuals, but in a single individual, the resting rate is a good index of the patient's progress. Sturgis and Tompkins[43] feel that a pulse rate at complete rest below 90 is seldom and that one below 80 is rarely associated with an increase in metabolism. This, of course, is of practical importance.

Boothby and Willius[44] in basal metabolism tests on patients suffering with primary cardiac disease, find that the level is slightly elevated in comparison to that of the normal but that in decompensated cases, there is a definite increase in the metabolism. They feel this is due to actual increase in muscular work required in labored respirations and also due to the subjective sensation of distress with resultant nervousness. DuBois[45] and Lev and Hamburger[46] report similar findings of increased metabolism in patients, suffering from primary heart disease and decompensation.

Germain Sèe,[47] in 1878, emphasized the fact that the association of irregularity of the heart with exophthalmic goiter had frequently been overlooked. This is probably what we today call auricular fibrillation. Bamberger[48] as late as 1919 collected only twenty-two cases of paroxysmal tachycardia in the literature. He mentions that irregularity of the heart was present and this, of course, would suggest paroxysmal auricular fibrillation. In 1918, Krumbhaar[49] reported fifty-one cases of toxic goiter studied with the electrocardiograph. He found four cases with sinus arrhythmia, three with ventricular extra-systoles, three with auricular fibrillation, one with auricular flutter and two with delayed conductivity. In 1922, Hamilton[50] found eighteen cases of auricular fibrillation in 200 cases of hyperthyroidism. He says that "very few cases of hyperthyroidism over fifty fail to show auricular fibrillation." Willius, Boothby and Wilson[13, 14] in 377 patients with thyrotoxicosis found constant auricular fibrillation in eight per cent and transient auricular fibrillation in nine per cent of the exophthalmic goiters; while in toxic adenomas, they found ten per cent in each group. They emphasized that the *duration* of the increased metabolic rate is most important in regard to development of auricular fibrillation. Phillips and Ander-

son[51] conclude that auricular fibrillation is the most common cardiac irregularity associated with hyperthyroidism and that it will usually disappear, if thyroidectomy is performed before the heart has been permanently injured. It is interesting to note that Stewart and Crawford[52] found experimentally on dogs that the heart is less efficient in the propulsion of blood, during irregular tachycardia than during the normal slower rhythm.

Willius, Boothby and Wilson found fifteen per cent of cases to have extrasystoles, which they feel have no significance in thyroid disorder. Paroxysmal tachycardia was not a common disorder in thyroid disease, occurring in about one per cent of cases.

Hoffman,[53] in 1914, was the first to describe high T-waves in the electrocardiograph tracings of patients, suffering with exophthalmic goiter. Krumbhaar[49] described an "unusually prominent T-wave in most cases of toxic goiter which, in about one-half of the cases, was markedly and persistently diminished after operation." Furthermore, he states that a diphasic or inverted T-wave, especially in Leads I and II, offers an unfavorable prognosis. Willius, Boothby and Wilson do not comment on the height of the T-wave except to call attention to the infrequency (one per cent) of inversion of the T-wave. This infrequence is due to the fact that degenerative changes in the myocardium are not common in hyperthyroidism. Hamburger[54] and his co-workers report several cases of their series as having a high T-wave which showed a definite lowering of the height when the thyroid was removed. Previous rest without iodine has no effect but with iodine a lowering of the T-wave in most cases is noted. They, however, found no uniformity in the increased height and concluded that it had little, if any, relation to pulse rate. It is well to remember in this connection that Rothberger and Winterberg[55] found in patients, having a marked accelerator tone, a high T-wave.

The association of hyperthyroidism and angina pectoris is rare. Lev and Hamburger[56] report six cases; Sturgis[58] reports one case. Hurxthal[15] found two cases with angina pectoris out of 500 cases of cardiac failure with hyperthyroidism. Haines and Kepler[57] remark that it is easy to overlook angina pectoris in the presence of severe hyperthyroidism, or mild hyperthyroidism in a patient with angina pectoris. A heart having a coronary supply which is sufficient under ordinary circumstances, may be inadequate to meet the demands placed upon it by the added work of the heart produced by hyperthyroidism and hence, the patient suffers pain. An interesting case, which recently came to my attention, was that of a patient with myxedema of, at least, ten years standing, with a minus metabolism of forty-three, who had a bundle-branch block and who suffered definite attacks of angina pectoris when she received over one and one-half grains of thyroid extract.

Sturgis[58] reports a similar case of myxedema with associated heart disease in whom attacks of angina pectoris were produced when more than one-half grain of thyroid extract was taken.

Recently, we have read many articles regarding cases of so-called "masked hyperthyroidism." It was Charcot,[59] in 1885, under the heading: "Maladie de Basedow: formes frustes," who called attention to a group of cases in which one of the triad of characteristic symptoms of exophthalmic goiter was missing. Chvostek,[60] in 1887, considered these formes-frustes cases as "symptom poor" cases in contrast to the well-developed typical cases. Levine and Sturgis,[61] in 1924, under the title "Hyperthyroidism Masked as Heart Disease," reported five cases. Priest[62], in 1926, reported three cases of hyperthyroidism, simulating primary heart disease. In 1928, Tucker[63] reported three cases of hyperthyroidism without visible or palpable goiter. Hamburger and Lev[64] report five cases, under the title of "Masked Hyperthyroidism." Freund and Cooksey[65] also report five cases of thyrotoxicosis, without visible or palpable thyroid. These patients are middle-aged individuals, who do not present the classical picture of hyperthyroidism, but who show a group of symptoms which, if analyzed, will place them in the hyperthyroid field. They have a staring expression of the eyes, an increased warmth, redness or pigmentation of the skin, increased restlessness and unexplained loss of weight, and come to the doctor with a complaint in one of the main systems, quite often cardiovascular. They have a persistent increased metabolism and under iodine medication or thyroidectomy, they improve or get completely well. This group must be kept in mind, as its ranks are increasing due to the added stress and strain which men and women over forty-five are now experiencing.

All of us have seen cases of hyperthyroidism which give no history of previous heart involvement and still have symptoms of heart failure. Hurxthal[15] studied 500 cases and came to the conclusion that the average age of congestive heart failure was above forty with a large percentage showing previous cardiovascular disease. He feels that "thyrotoxicosis has a specific excitatory effect on the heart and that this, more than the demands for increased work, produces failure in a heart weakened by the degenerative processes of age." In his opinion, the most significant causes of congestive heart failure in hyperthyroidism are age and its accompanying cardiovascular changes, the specific heart drive, auricular fibrillation, and the duration and intensity of thyroid activity. Andrus[66] feels that when congestive heart failure appears under forty that there must be "a pre-existent rheumatic or more rarely a syphilitic heart disease." If you will review your own cases, you will be struck by the fact that the majority of these congestive heart-failure patients were older individuals, who, for many years, had adenomatous thyroids with secondary hyperthyroidism. These patients usually give a history of many exacerbations and remissions.

A review of this kind would certainly lack completeness, if I did not discuss a condition more prevalent than even thyrotoxicosis. I mean the syndrome of neuro-circulatory asthenia or "effort syndrome" as it affects the cardiovascular tree and which might even be mistaken for a toxic thyroid

heart. You can well imagine the difficulty in diagnosis when such a patient has an associated enlarged thyroid.

Addis and Kerr[67] examined many recruits, during the war, and found these embryonic soldiers were complaining of increased pulse rate, tremor, and of cold, moist hands which became cyanosed when dependent. They even complained of precordial pain with dyspnea and palpitation on moderate exertion, dizziness, flushing and fainting. This condition was found both in patients who had normal-sized thyroids and those who had enlarged thyroids. Addis and Kerr felt that the thyroid had no etiologic relationship to the nervous picture. Plummer, though, feels that these patients with neurocirculatory asthenia are more prone to thyroid enlargement than are normal individuals.

Remember, in this condition, that this tachycardia disappears with rest and sleep. Dell' Acque and Aschner[68] noted in hyperthyroidism that the average pulse rate increased 4.82 upon changing from a reclining to a standing posture, while in neurotic patients, it was five times as great, namely, 25.3. This might be a good diagnostic point. Peabody and his co-workers[69] found that the basal metabolism was normal in soldiers with so-called "irritable" hearts and furthermore they were impressed with the fact that these patients showed a marked tachycardia, easily provoked by mental or physical strain, which disappeared when they were allowed to lie down for a short period.

Summary

Parry should be given credit for first describing thyrotoxicosis and especially so its cardiac manifestations. The fact that cardiac complications, in young people, are infrequent; the fact that severe intoxications give no clinical picture of decompensation in previously undamaged hearts; the fact that after complete relief, by thyroidectomy in previously undamaged hearts, there is a complete return of normal cardiac findings, all tend to uphold the opinion that hyperthyroidism does not cause permanent myocardial changes. As the so-called "irritable heart" in neurocirculatory asthenia approaches in symptomalogy the heart in thyrotoxicosis, we must not lose sight of the variations in tone of the vagus and sympathetic nerves, which might play a cardinal rôle. In a practical consideration of this topic, it is well ever to keep in mind that hyperthyroidism does cause marked subjective heart symptoms.

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Editorials

THE PROGRAM FOR THE GENERAL SESSIONS OF THE SIXTEENTH ANNUAL CLINICAL SESSION IN SAN FRANCISCO

In the week of April 4, 1932, will occur one of the great medical meetings of the year. The Annual Session of the College has become a focal point for those interested in the medical, as contrasted with the surgical, interests of our profession.

That the College is meeting a need in medicine on this continent has been attested by its remarkable growth in numbers and in influence during its relatively short existence, and particularly during the period of less than a decade following its reorganization. The College stands today as representative of those practitioners who are concerned with both the science and the art in medicine, as the American College of Surgeons is a meeting ground for those concerned with the surgical specialties. The College has not attempted, nor has it manifested at any time a desire, to invade the fields so well cultivated by the American Medical Association, The American Hospital Association, The Association of Medical Colleges and other associations formed for promotion of their own various interests. The primary purposes of the College are the encouragement and preservation of high standards, the dissemination of knowledge within its field and the cultivation of the historic and esthetic ground in which medicine, as one of the learned professions, grows. There is no desire to set the members of the College apart from other medical men, but there is clearly shown a desire to stimulate all men in medicine to the level of professional, ethical and cultural achievement at which fellowship in the College is possible.

Each session of the College has reflected the purposes and ideals thus briefly stated. The San Francisco Session will be the first to be held beyond the Mississippi. While the United States census has shown in recent decades only a slow movement of the center of population westward along the thirty-ninth parallel, located now in southwestern Indiana, there has been a remarkable development, not only in population, but also in power, in influence and in culture along the entire Pacific Coast. Here a people from the same ethnic sources and with, in general, the same cultural and political purposes as found in our population eastward has accumulated. But this people has a genius of its own. There is a freshness in its point of view, an exuberance in its spirit, and a capacity for building great industries and noble institutions that set it somewhat apart, due, no doubt, in good measure to its sea and valley and mountain. San Francisco occupies a position near the center of this great

empire and this makes it a fitting seat for the first meeting of the College to be held within its bounds.

Two great medical schools form the nucleus of an important medical center. The medical school of the University of California, with the Hooper Foundation for Medical Research, and the Stanford University Medical School are known the world over. These institutions, with their laboratories and hospitals, together with all other medical facilities around and about the Bay of San Francisco, have been placed at the disposal of the College for the week of the meeting. Each morning, on Tuesday, Wednesday, Thursday and Friday, clinics and demonstrations will be held in which the advanced work in these institutions will be exemplified. As is customary, each member of the College will be given an opportunity, long in advance of the meeting, to choose the places he desires to visit and the men and subjects he wishes to hear. This is arranged from the office of the Executive Secretary of the College and the early disposal of this matter, which might otherwise be confusing, lends order to this part of the program. The arrangement of the laboratory and clinical portion of the program is in the hands of Dr. Wm. J. Kerr, Professor of Medicine in the University of California, who is general chairman for the Session. This will be the second meeting in which the President of the College has been responsible for the program of the general sessions, attended by all fellows, associates and guests, and in which all the formal papers and addresses are presented. There will be five afternoon and two evening sessions of this character. On Monday the short introductory program of welcome will be followed by scientific papers. On Monday evening a program of extraordinary interest will be presented. On both Tuesday afternoon and evening the scientific sessions will continue, while on Wednesday, Thursday and Friday, only the afternoons will be thus occupied, Wednesday and Thursday evenings being given over to the convocation and the banquet.

For the seven afternoon and evening sessions set aside for the presentation of scientific and practical matters before the entire group, a program of outstanding merit with some unique features is being arranged. This seemed to your President to be an opportunity for the exposition of the best medicine on the Pacific Coast. Men deemed capable of sound and scientific presentation have been invited to take part and their response has been very gratifying. The members of the College will thus have an opportunity to see and hear a remarkable group not so commonly seen and heard when the programs are given farther east. This opportunity of contact with men about whose work we know and yet with whom contact has not been as frequent as desired will be a feature of great value and interest.

While there is an unusual number of new names on our program, both from the coast states and from the country at large, the outstanding names in medicine will be well represented. This is not the time nor place to detail names and subjects but it may be said that a program of wide

range and interest has been arranged. Final selection of many offerings is still to be made. Experience has shown that not more than about fifty papers and addresses can be well presented in the allotted time, giving fifteen to twenty minutes to each presentation, with an occasional extension of time when the interest of the subject requires it.

Even to suggest the wide range of subjects offered would be difficult, but the appearance of certain trends in modern medicine makes this attempt worth while. There will be the study of the physics and physiology of arteriosclerosis and hypertension by a master. Pulmonary arteriosclerosis and the congenitally narrowed aorta have a place. The onset of decompensation of the heart in elderly patients, a follow-up study of hypertension, and an experimental and clinical study of the effect of hypothroidism upon the heart with two studies of an extensive material, one on cardiovascular syphilis and one on the electrocardiograms, will give valuable contributions to our knowledge of the heart and blood vessels. The lungs and bronchi are studied from several angles. Atelectasis and tuberculosis, the treatment of cavities, some observations on pulmonary emphysema and the rôle of bacteria in asthma will be among the subjects of unusual interest. The liver will receive attention with subjects ranging from the effect of the administration of glucose and insulin on the glycogen content, to an unusual study of primary carcinoma of the liver in Chinese. As to the kidneys, there will be studies of clinical and of pathological differentiation in Bright's disease and a study of the relationship of nephritis and nephrosis.

The practical applications of recent discoveries in the field of gastro-intestinal physiology, the absorption of sugar from the intestinal tract, the clinical aspects of gastric secretions, and the elements of error in diagnosis in jaundiced patients are to be discussed. On the subject of the adrenal glands, there will be presentations of unusual significance from both the experimental and clinical standpoints. The biological and clinical importance of ovary-stimulating substances will be brought out. There will be a study of calcium metabolism and diseases of the parathyroid gland. Recent studies on the chemical pathology of epilepsy and on its treatment appear. We will learn something more of the mechanism of edema formation in disease. There is a study of leukopenia, on the action of benzol, roentgen rays and radium on the blood and blood-forming organs; on the relation of paranasal sinus infection to disease elsewhere; on the clinical significance of the atrophic tongue; and on the experimental basis for vaccine treatment of chronic arthritis with a summary of results of treatment. There will be studies on the chemotherapy of amebiasis, together with a consideration of human amebiasis.

While there will be many groupings of papers on allied subjects, symposia do not constitute an outstanding feature of the program. One symposium, however, will make up for the lack of many others. Recent years have seen an almost unbelievable advance in our knowledge of the involuntary nervous system. Not only have the anatomists

been able to construct a fairly comprehensible picture of it, but the physiologists have delved deeply into its function in many species of animals and very recently have added greatly to our knowledge of hormonal control. Pituitary hormone, adrenalin and acetyl cholin have been subjected to such intensive study that their actions are becoming quite thoroughly known. Much has been learned recently of the sympathetic control of the kidneys and of blood pressure, of the peripheral vessels, of the gastro-intestinal tract and of the urinary bladder. Even as this knowledge has been developing, surgery has been making use of it. It, therefore, seems that a symposium on the involuntary nervous system, which would bring together the anatomist, the physiologist, clinicians in medicine, and surgeons, would be of the most profound interest. If you think of the names of the men you would most wish to hear on these subjects, you will be likely to find them on the program when it is finally announced. An outstanding anatomist in this field, and the two greatest physiologists in this country, are on the program for this symposium.

The history of medicine has been given a place on previous programs, notably that of the Minneapolis meeting, and approval of this feature by the Fellows has been very general. At this time of unrest and uncertainty, affecting medicine as it does all other walks of life, an address on medicine in Utopia will be particularly appropriate. Many books on Utopia have been written and the relation of the ideas about medicine in that happy land will have an immediate interest. There is a lively story on medicine on the Pacific Coast and it is hoped that this can be made available.

Many other items of interest are on the program but this will suffice to show that the program of the General Session of the San Francisco meeting promises to reach the high standards set in recent years. The opportunity of securing low rates of travel to the coast, the extension of time customary for travelers to this region, the opportunity either preceding or following the meeting for vacations in the land of sunshine and flowers, should make the San Francisco Session one of the most attractive we have ever held. Subsequent issues of the ANNALS will give all the details of arrangement and of the program. It is to be hoped that all Fellows will give a ready response to the efforts of our California hosts.

S. M. W.

THE SASKATCHEWAN EXPERIMENT

In Saskatchewan, and to a less extent in Manitoba, there is in operation a "municipal doctor" system which is intended to solve the problem of obtaining good medical care for the residents of certain rural communities. The character of this system with its policies and procedures is the subject of the eleventh publication of the Committee on the Cost of Medical Care, by C. Rufus Rorem. The rural municipality, composed of nine townships, is entirely apart as a unit of government from such cities, towns or villages as may be situated within its area. Each

rural municipality is a unit for administrative purposes, including the levying of taxes. In Manitoba there are three, and in Saskatchewan there are twenty municipalities which employ full-time physicians and levy taxes to pay for this service. Twelve others make grants of $1,500 or less as inducements to physicians to practice in their communities, and as remuneration for services as public health officers and for the care of indigent persons. The median salary of the twenty full-time municipal doctors in Saskatchewan is $4,000. Each serves an average population of about 1800, receives from 1,000 to 1,500 office calls annually, and makes from 300 to 500 visits to the homes of patients. Notwithstanding the full-time status, opportunity is provided in nearly all cases for the municipal physician to earn additional income from special services. In some instances he is directed to make nominal charges for specified services. An interesting example of these is a fee for the "initial" house visit in any illness. Apparently the object of this is to discourage house calls for minor conditions which could be properly treated at the office. Most of the municipalities levy taxes upon the basis of the value of farm lands and the municipal physician levy usually amounts to between $7.50 and $10.00 per family. Arrangement is usually made by which transients and residents not eligible to the service may be treated upon a fee basis. The doctors themselves say that while they do more work they also receive a larger net income than could be earned by private practice in the same areas, partly because there are no "bad debts." Certain advantages and disadvantages of this entire system, which is fundamentally merely contract practice, are obvious. Opposition has come largely from non-resident landowners, from well-to-do farmers with small families, and from those living close to the doctor's office. Independent physicians in towns included within the areas of the rural municipalities using this system and in adjacent communities recognize that the presence of municipal physicians has had unfavorable economic effects upon their practice; and private physicians in Saskatchewan on the whole express disapproval of the system, although they admit that in certain rural areas it may be the only way to assure the continued presence of a medical practitioner. This, as well as other modifications of the time-honored relationship between physician and patient in private practice, should receive careful attention and study. Whether his initial reaction is one of strong disapproval or not, the medical man of today can ill afford to be indifferent to such tentative schemes for altering medical economics. Rather should he study and weigh each of them that he may be prepared to exercise a constructive directing influence if occasion arises. If modifications are ever found necessary, they should originate within the medical profession itself, and not be foisted upon it. They should represent the best constructive thought of which the medical mind in capable. Only through such active participation in the economics of public health can the medical profession hope to uphold those high standards of practice which are absolutely essential.

ACCIDENTAL INJURIES AND OCCUPATIONAL DISEASES

In a recent decision, the Tennessee Supreme Court (Morrison vs. Tennessee Consolidated Coal Co., 39 S.W. (2nd) 272; decided June 10, 1931) holds that there is no recourse under the workmen's compensation act for a disease, occupational or otherwise, unless that disease naturally results from an accidental injury. Further "an injury to be regarded as an accidental injury under the compensation act, must be an injury unforeseen, unexpected, and fortuitous. An element of unexpected casualty must be present." Likewise, the origin or inception of the disease must be assignable to a determinate or single occurrence identified in space or time, it was pointed out. This decision is seemingly in accord with the general usage of the terms in the statutes and probably rightly interprets the spirit of the earlier phase of the movement to insure compensation for occupational injuries. However, it should attract attention to the fact that there is a general tendency to apply the principle of compensation more broadly than the original intent of the law. In addition to those occupational injuries which are accidental in the sense defined in the decision to which reference has been made, many now consider it both proper and desirable that compensation should be paid for those injuries which grow out of the long continued operation of the causes of occupational disease. Here the situation is somewhat different. In many instances, instead of the element of the unforeseen, unexpected and fortuitous casualty being present, the worker has entered upon his employment in full knowledge that a hazard existed and has elected, although it may be under the stress of necessity, to expose himself to that hazard. One must feel in accord with the desire to give such workers compensation, especially when they have not been made aware of the hazards existing. It would seem, however, that cooperative insurance with the cost apportioned between the employer and the employed more justly meets the needs of this group. At least, it is highly desirable that statutes providing compensation for occupational injuries and occupational diseases be so framed as to discriminate between the various classes of those entitled to the benefits which are provided.

Abstracts

The Etiology of Gall Stones. I. Chemical Factors. By RUDOLPH SCHOENHEIMER and LEO HRDINA. (Proc. Soc. Exp. Biol. and Med., 1931, xxviii, 944-945.)

The problem of gall stone formation is the problem of the precipitation of cholesterol out of the bile. The question has been investigated as to whether the ability of bile to hold cholesterol in solution might be due to some one or all of the bile acids. It was found that the precipitation of bile acids from human bile by ferric chloride, by lead acetate, or by any other means produces a simultaneous precipitation of cholesterin. The complexes of bile acids and cholesterol are readily soluble in water and may be purified without lessening the cholesterol content. Large amounts of these complexes have been isolated from human bile in which it appears that all or nearly all of the cholesterol is thus bound. In dog or ox bile, on the contrary, most of the bile acids are in combination with fatty acids rather than cholesterol. This explains the complete absence of cholesterol-containing gall stones in these animals. As for man, this investigation shows that whenever the organism by any pathological processes brings about a significant lowering of the bile acids in the gall bladder in relation to the amount of cholesterol in it, precipitation of cholesterol is bound to occur.

The Etiology of Gall Stones. II. Rôle of the Gall Bladder. By EDMUND ANDREWS, RUDOLPH SCHOENHEIMER and LEO HRDINA. (Proc. Soc. Exp. Biol. and Med., 1931, xxviii, 945-946.)

Under normal conditions the gall bladder mucosa, in its concentrating effect upon the bile, is able to absorb water rapidly; while bile salts and cholesterol, if they are absorbed at all, are absorbed at an equal rate. Under such conditions there is no danger that there will not be enough bile salts to hold the cholesterol in solution. In a series of experiments in which the cystic duct was ligated, leading to infection of the gall bladder, with added traumatic insult, the action was diametrically opposite in respect to differential absorption. In every case an increase in the concentration of cholesterol was found, averaging + 29 per cent, and a lessening in the concentration of the bile salts, averaging — 28 per cent, was found. The ratio of bile salts over cholesterol was 97 for normals and 59 for sixteen experiments. This change is sufficiently marked to cause precipitation of cholesterol if continued for any length of time. Apparently the gall bladder mucosa has great absorptive power for bile salts if diseased.

The Etiology of Gall Stones. III. Bile Salt-Cholesterol Ratio in Human Gall Stone Cases. By EDMUND ANDREWS, RUDOLPH SCHOENHEIMER and LEO HRDINA. (Proc. Soc. Exp. Biol. and Med., 1931, xxviii, 947-948.)

The two preceding studies having suggested that cholesterol stones are found in the human gall bladder because there are not enough bile salts present to hold the cholesterol in solution, one would expect to find in human gall bladders with cholesterol stones a lesser quantity of bile salts. Results of analyses confirm this expectation. In a group of operated cases the bile salt-cholesterol ratio was found to average 3.4, and in the mixed bladder bile from 30 examples of cholelithiasis found post-mortem this ratio was 0.6. The control series of Newman on normal human gall bladders gave a bile acid-cholesterol ratio of from 10 to 24 and Hammarsten found ratios of 10 and 40 respectively in two cases of sudden accidental death. These figures add further proof to the theory that cholesterol stones are due to a faulty differential absorption of bile acids and cholesterol by the abnormal gall bladder mucosa.

Lead Poisoning in Brass and Bronze Foundries. By FRANK G. PEDLEY, M.D., D.P.H. (The Canadian Med. Assoc. Jr., 1931, xxv, 299-303.)

Lead poisoning is an important hazard in certain types of bronze foundries. Bronze is essentially an alloy of copper and tin, and brass an alloy of copper and zinc. However, this distinction is not always observed in naming alloys. Lead is frequently added to both, sometimes to improve them, sometimes to cheapen them. In railroad bronzes, such as bearings, the antifrictional qualities of lead make it a valuable constituent and it may be present in amounts as high as 20 per cent. The hazard arises in part through the volatilization of lead at the temperature necessary to insure the melting of the copper constituent in the preparation of the alloy and during the subsequent pouring of the molten alloy; and, in part, from the subsequent grinding and polishing of the castings. Of 38 men engaged in the founding of high lead bronze, 24 were found to be suffering from acute lead poisoning, nine others showed definite evidence of lead absorption, and only five showed no evidence of plumbism. Three brass polishers who succeeded each other on the same emery wheel became poisoned with lead. Blood smears were examined from 26 men engaged in polishing low lead brass and bronze (less than six per cent lead). Five of these showed stippled cells in a number well in excess of 200 per million red cells. It is the belief of the author that lead plays an important part in the disease pictures variously diagnosed as brass poisoning, bronze poisoning, and copper poisoning.

The Relation of Heredity to the Occurrence of Spontaneous Leukemia, Pseudoleukemia, Lymphosarcoma and Allied Diseases in Mice; Preliminary Report. By MAUD SLYE. (Am. Jr. of Cancer, 1931, xv, 1361-1385).

The familial occurrence of human leukemia and of the related lymphatic diseases has been noted repeatedly. While the data in each individual report are few, they are all in agreement in indicating that in man the leukemic diseases have an hereditary basis and tend to run in families; and, further, that they tend to occur in cancer strains. Dr. Slye found 975 examples of the leukemic diseases in the first 50,000 mice autopsied by her. The division between the sexes was practically equal. All instances of leukemia, pseudoleukemia, and lymphosarcoma were in families carrying other forms of malignancy. All occurrences of these diseases have been in a limited number of strains of mice. Whole races of mice of other derivation, but living for many generations under identical environmental conditions, have been entirely free from these conditions. The difficulty in certain recognition and differentiation of members of this group of diseases by histopathological methods is fully recognized; yet the results obtained furnish both negative and positive evidence for the assumption that the tendency to these diseases and the absence of these diseases are both subject to the control of heredity. Likewise, since the leukemic diseases were found to occur in cancer strains only, there is strong evidence in support of the view that the leukemias, pseudoleukemias, and lymphosarcomas are members of the neoplastic group.

Tumor Immunity. By THOMAS LUMSDEN, M.D. (The Am. Jr. of Cancer, 1931, xv, 563-640.)

From extensive experimentation with several strains of transplantable tumors, Lumsden believes that it may be safely concluded that anti-malignant-cell bodies, lethal to cancer cells but harmless to normal tissue cells, can be produced. When an implanted tumor already established in the body is gradually destroyed by injecting antiserum or formalin into it, active immunity against the tumor is induced by a mechanism which may be called autovaccination. It has still to be learned whether similar effects can be obtained with spontaneous tumors, in which the relationship between host tissue and invading tissue may be quite different.

Reviews

The Pathology of Internal Diseases. By WILLIAM BOYD, M.D., M.R.C.P., Ed., Dipl. Psych., F.R.S.C.; Professor of Pathology in the University of Manitoba; Pathologist to the Winnipeg General Hospital, Winnipeg, Canada. xvi + 888 pages. 298 illustrations. Lea and Febiger, Philadelphia, 1931. Price, $10.00.

This is a companion volume to the author's Surgical Pathology, with only a minimum of unavoidable overlapping between the two. It aims to present the pathology of those diseases which are found in the medical wards of a teaching hospital and to relate their signs and symptoms to deviations from the normal in morphology and function. In this it succeeds admirably. Naturally no one pair of book covers can enclose all of the material which the subject foreshadows. Certain gaps must occur. Certain infectious diseases, diseases of special importance in the tropics, and others in regard to which no clear cut pathological picture has been established, have been intentionally excluded. In many respects the choice of material has been made with great skill. Throughout, special attention is given to presenting the newer knowledge in pathology, not that which is so new as to be ephemeral, but the very things which, although well established, the internist will find entirely wanting or very sketchily given in his older books. This is a pathology text of intriguing interest for the upper class student and the practitioner whose interest is not with the fundamental tissue lesions as such, but with the pathological processes of individual disease conditions. The reviewer finds himself very often in sympathetic accord with the point of view of the author in various matters that are not accepted by all. For instance, the fact that endocarditis in its various forms and etiologies is a fairly well unified series is clearly emphasized; so-called acute massive collapse of the lung is not considered a condition *sui generis* but merely a special manifestation of pulmonary atelectasis, and toxic adenomas of the thyroid and exophthalmic goiter are grouped under the heading of Graves' disease. However, it is not because of general agreement with its subject matter that the writer commends this work. It is rather because he realizes its splendid usefulness as a text in special pathology, as collateral reading in internal medicine, and as a reference book for the practitioner who wishes to keep up with the advances in pathology.

Deep X-Ray Therapy in Malignant Diseases: A Report of an Investigation Carried Out from 1924-1929 under the Direction of the St. Bartholomew's Hospital Cancer Research Committee. By WALTER M. LEVITT, M.B., D.M.R.E., Medical Officer in charge of the Radiotherapeutic Research Department. With an introduction by SIR THOMAS HORDER, Bart., K.C.V.O., M.D., F.R.C.P., Chairman of the Cancer Research Committee. 128 pages. John Murray, London, 1930. Price, 10 s. 6 d., net.

This report gives the technical methods employed and the results obtained during the several years that the St. Bartholomew's Cancer Research Committee (formerly the Radiotherapeutic Research Committee) has been actively engaged in the treatment of malignant disease by irradiation. Two main types of therapeutic technic were developed: (1) intensive single-dose technic in which the entire dosage is applied in one, or at the most in two or three days; and (2) intensive split-dose technic in which the dose is applied in several fractions at intervals of approximately 24 hours over a period of several days. The

number of fractions varies from 6 to 30. In 85 cases radium was used in addition to x-rays. So different are the results obtained in carcinoma of various regions that mass statistics are without meaning, and when split up into the necessary groups, the total number of cases in each is not large enough to be impressive. However, a certain degree of encouragement is afforded. Of 43 cases of inoperable carcinoma of the breast, 6 were still living at the time of report without signs of cancer present. In three of these, three or more years had elapsed since treatment. Thirteen of 60 cases of malignant disease of the uterus, chiefly carcinoma of the cervix, were reported alive without evidence of growth present. This was true also of 27 out of 170 cases of malignancy of the upper air passages. In the portion of this group suffering from carcinoma of the tonsil, the results were uniformly poor. Twenty-six cases of malignancy of the rectum were treated in the period under review, and of these only one was without evidence of the disease. In about 29 per cent of all cases treated, x-rays failed to have even a palliative effect; and in a further 22 per cent only minor degrees of improvement were observed, or improvement was of but short duration. In view of the statistical results, the conclusions stated in this report seem somewhat too sweeping, as being true of but a limited proportion of the cases. One must remember, however, that these patients were considered inoperable; and any salvage of human life or even temporary return to a state of economic independence, is something gained.

Resistance to Infectious Diseases: An Exposition of the Biological Phenomena Underlying the Occurrence of Infection and the Recovery of the Animal Body from Infectious Disease, with a Consideration of the Principles Underlying Specific Diagnosis and Therapeutic Measures. By HANS ZINSSER, M.D., Professor of Bacteriology and Immunity, Medical School, Harvard University; formerly Professor of Bacteriology at the College of Physicians and Surgeons, Columbia University, and Bacteriologist to the Presbyterian Hospital, New York; formerly Professor of Bacteriology and Immunity, Stanford University, California. Fourth edition, completely revised and reset. xviii + 651 pages. The MacMillan Company, New York, 1931. Price, $7.00.

Under this new title appears the fourth edition of Zinsser's Infection and Resistance. Advances which have been made in the eight years since the third edition came out have produced profound modifications in the theories of immunology and consequently in their application to methods of diagnosis and therapy. Many chapters have required rewriting in order to introduce new material and to eliminate that which has been discarded. The first section of the book, 486 pages, deals with fundamental conceptions and theories, while the second section discusses the problems of immunology as applied to individual infectious diseases. While the first portion of this book is indispensable to the teacher and laboratory worker, the second section will be of interest and value to the practitioner. Here are found full discussions of immunity in syphilis and tuberculosis, and of the applied principles of immunization in scarlet fever, pneumonia, typhoid and paratyphoid fever, meningitis, rabies, plague, cholera, anthrax, influenza, small pox and various other infectious diseases. This book can be heartily recommended to those who seek a comprehensive and authoritative text on immunology. Numerous bibliographic references, arranged as footnotes, give the sources of material other than that by the author. It is unfortunate that many of these references lack the page number, a very important aid after journals have been bound.

Food Allergy: Its Manifestations, Diagnosis and Treatment with a General Discussion of Bronchial Asthma. By ALBERT H. ROWE, M.S., M.D., Lecturer in Medicine in the University of California Medical School, San Francisco, Calif.; Chief of the Clinic for Allergic Diseases of the Alameda County Health Center, Oakland,

Calif., etc. xi + 442 pages. 1931, Lea and Febiger, Philadelphia. Price, $5.00 net.

Forty-three per cent of 400 unselected individuals were found to give a family history of allergy; and a personal history of allergy occurred in thirty-five per cent of this group. In general, statistics show a probable food allergy in upward of thirty per cent of all persons. In the monograph under review the author treats this important subject in an extremely complete manner. The many diverse characteristics and manifestations of food allergy are described as they affect the gastro-intestinal system or result in bronchial asthma, eczema, urticaria or angioneurotic edema. Diseases less commonly related to allergy in diagnosis such as migraine, neuralgia, arthritis, bladder allergy, etc., are also considered. The frequency of negative skin reactions is emphasized and the method of "elimination diets" which was devised by the author is fully set forth as applied to both diagnosis and treatment. All internists will be interested in the section on the allergic aspects of drug sensitizations. This monograph is admirable in its completeness, in its scientific approach and in the reserve with which a subject has been handled, which might easily have led a specialist to make extravagant and unsupported generalizations. An extensive bibliography is provided.

Recent Advances in Cardiology. By C. F. Terence East, M.A., M.D. (Oxon.), F.R.C.P. (Lond.), Junior Physician, King's College Hospital; Physician, Woolwich Memorial Hospital; Sometime Radcliffe Travelling Fellow, University College, Oxford; and C. W. Curtis Bain, M.C., M.B. (Oxon.), M.R.C.P. (Lond.); Physician, Harrogate Infirmary. Second edition. x + 353 pages. 10 plates and 62 text-figures. P. Blakiston's Son and Co., Inc., Philadelphia, 1931. Price, $3.50.

This is the second edition of the Cardiology member of the Recent Advances series. In clear and concise form it presents the present day knowledge of its subject. Certain sections have been entirely rewritten in this edition. Much attention is given to electrocardiographic findings throughout, and one chapter is devoted entirely to this method of examination. To the reviewer the presentation of myocardial syphilis seems entirely inadequate, for only the extremely active diffuse form is considered. The final chapter on the interpretation of certain misleading physical signs and symptoms which may be encountered even in those with presumably healthy hearts is especially important in connection with routine physical examinations. For the practitioner this will prove an extremely useful manual.

Lane Lectures on Pharmacology: By Walther Straub, M.D., Ph.D. (h.c.), Professor of Pharmacology, University of Munich. (Stanford University Publications, University Series, Medical Sciences, Volume iii, Number 1). 88 pages, 9 text-figures. Stanford University Press, Stanford University, California, 1931. Price, postpaid, paper $1.00; cloth, $1.50.

Professor Straub chose as subjects for his six Lane Lectures, delivered in San Francisco in April, 1929, the following: Intoxicating Drugs, Ways to Ideal Anesthesia, Digitalis—Chemistry, Digitalis—Biochemistry, General Pharmacology of Heavy Metals, Camphor and the Modern Analeptics. These topics are discussed in an interesting and thought-provoking, rather than an exhaustive, manner. An index is provided.

Hemorrhoids: The Injection Treatment and Pruritus Ani. By Lawrence Goldbacher, M.D., Philadelphia. Second edition. 207 pages, 31 illustrations. F. A. Davis Company, Philadelphia, 1931. Price, $3.50 net.

This second edition of a manual on the treatment of hemorrhoids and pruritus ani by the injection method gives several changes in technic as compared to the first edition. The author's instruments and method of using 5 per cent phenolized oil are clearly set forth. Etiology, pathology and symptomatology are adequately pre-

sented and the book is well-printed and well-indexed.

Rheumatic Fever—A Heart Disease. By JOHN L. CHESTER, M.D., F.A.C.P., Attending Physician and Lecturer to the Training School, Providence Hospital, Detroit; Attending Physician and Chief of the Heart Service, Eloise Hospital, Eloise, Michigan. 122 + 4 pages. Privately printed, 1929.

This is a concisely written monograph bringing together the best of recent advances in the field of rheumatic cardiac disease. It is illustrated by case reports from the cardiac service of Dr. F. N. Wilson at the University of Michigan Hospital, Ann Arbor.

Lehrbuch der allgemeinen Physiologie. Edited by ERNST GELLHORN, Ph.D., M.D., formerly Professor of Physiology at the University of Halle, Associate Professor of Physiology at the University of Oregon, Eugene, Oregon. xiii + 741 pages, 126 illustrations. George Thieme, Leipzig, 1931. Price, in paper, M. 47; bound, M. 49.50.

In the preparation of this textbook of general physiology the editor named has had the aid of Professors Asher of Berne, von Buddenbrock of Kiel, Oppenheimer of Berlin, and Spek of Heidelberg. It treats physiology more particularly from the standpoint of recent advances in physical-chemistry. It should prove valuable to the more advanced students in the related fields of general biology, embryology and pathology, as well as to the physiologist.

Die Bakteriologie der Wurmfortsatzentzündung und der appendikulären Peritonitis. By W. LÖHR, Madgeburg, and L. RASSFELD, viii + 96 pages, 46 illustrations and 11 tables. George Thieme, Leipzig, 1931. Price in stiff paper cover, M. 12.

This well-arranged monograph deals with the bacterial content of the healthy and of the diseased appendix. It is based very largely upon original work consisting of cultural studies of appendices in sufficiently large series to make the results of significance. It is an important contribution to the subject of peritonitis of appendiceal origin.

College News Notes

Dr. William Gerry Morgan (Fellow), Washington, D. C., during the latter part of August was unanimously elected Dean of the Georgetown University School of Medicine by the University directors. Dr. Morgan will continue to serve as a Regent of the University, to which position he was appointed last June. For many years, Dr. Morgan has served on the medical faculty of Georgetown University. Dr. Morgan succeeds the late Dr. John A. Foote, who died several months ago. Dr. Morgan is the member of the Board of Governors of the American College of Physicians representing the general profession of the District of Columbia.

At a recent meeting of the Board of Managers of the Goshen Hospital, Goshen, N. Y., Dr. Louis F. Bishop (Fellow) was appointed consulting cardiologist of the staff of consultants of the Goshen Hospital.

Dr. E. J. G. Beardsley (Fellow), Philadelphia, addressed the Lehigh County Medical Society at Allentown, Pa., September 8, on "The Importance of Routine in Medical Diagnosis."

Dr. Roy C. Mitchell (Fellow), Mount Airy, N. C., presented a paper on the "Early Diagnosis of Carcinoma of the Stomach" at the meeting of the Eighth District Medical Society of North Carolina, October 2.

The Interstate Postgraduate Medical Association of North America held its annual meeting at Milwaukee, October 19-23, under the presidency of Dr. Henry A. Christian (Fellow), Boston, Mass.

Dr. Edwin Henes, Jr. (Fellow), Milwaukee, is Secretary of the above Society.

Under the Presidency of Surgeon General Hugh S. Cumming (Fellow), U. S. Public Health Service, Washington, D. C., the American Public Health Association held its annual meeting in Montreal, Que., September 14-17.

Dr. J. Feigenbaum (Associate) addressed the Montreal Clinical Society on September 9, 1931, upon the subject of "Constitution and Disease, Relating Particularly to Types Encountered in Peptic Ulcer, Gall Bladder Disease, Hypertension, and Exophthalmic Goiter."

Dr. Frederick T. Lord (Fellow), Boston, Mass., was elected president of the American Association for Thoracic Surgery at the fourteenth annual meeting held recently in San Francisco.

Dr. E. J. G. Beardsley (Fellow), Philadelphia, addressed the Washington State Medical Association at Aberdeen, Washington, August 3, on "Cardiovascular Disorders of Every-day Practice." Dr. Beardsley also held a clinic at the St. Joseph Hospital, Aberdeen, on the morning of August 4.

Dr. Howard L. Hull (Fellow), Elma, Washington, who has charge of the Oakhurst Sanitarium for Tuberculosis, acted as host to Dr. Beardsley during his stay in the Evergreen State.

Dr. R. L. Hamilton (Fellow), Sayre, Pa., was among those who addressed the American Heart Association at its meeting in Philadelphia on June 9. Dr. Hamilton's subject was "Precordial Pain: Its Causes and Significance."

Dr. Hyman I. Goldstein (Associate), Camden, N. J., is the author of the article,

"Sterile Live Maggots in the Treatment of Osteomyelitis and Tuberculosis Abscesses," which appeared in the July, 1931, issue of Medical Review of Reviews. Dr. Goldstein also has an article appearing in the September, 1931, issue—"Heredo-Familial Angiomatosis."

Dr. James L. McCartney (Fellow), formerly Director, Bureau of Mental Hygiene, Connecticut State Department of Health, has been appointed psychiatrist with the New York State Department of Correction, and is stationed at the New York State Reformatory, Elmira, New York.

Dr. LeRoy S. Peters (Fellow), Albuquerque, N. M., presented a paper before the Los Angeles County Medical Society and the Hollywood Academy of Medicine on August 20.

Dr. Wann Langston (Fellow), Oklahoma City, Okla., has resigned as Superintendent of the University Hospital to become Professor of Clinical Medicine in the University of Oklahoma School of Medicine on a part-time basis. Dr. Langston has opened his office at 502 Medical Arts Building for part-time practice in internal medicine.

Dr. Daniel E. S. Coleman (Fellow), New York, N. Y., is the author of an article, "Materia Medica—A Plea for Better Therapeutic Teaching," appearing in the August, 1931, issue of the Hahnemannian Monthly.

Dr. H. Beckett Lang (Fellow) has been appointed Clinical Director of the Marcy State Hospital at Marcy, New York.

Dr. Albert Warren Ferris (Fellow), after serving as Senior Assistant on the Staff of the Glen Springs, Watkins Glen, New York, for fifteen years in two terms of service, has retired from practice and resides at 111 N. Walnut Street, East Orange, N. J. Dr. Ferris was previously President of the New York State Commission in Lunacy, and Medical Editor of the International Encyclopedia.

A medical clinic on Sero-fibrinous Pleurisy held by Dr. Carl V. Vischer (Fellow), Philadelphia, Associate Professor of Medicine at the Hahnemann Medical College, was published in the current issue of the Hahnemannian Monthly.

Major Edgar Erskine Hume (Fellow), Medical Corps, U. S. Army, stationed at the Adjutant General's Office, State House, Boston, Mass., was under President Hoover's appointment, Secretary of the American Delegation to the International Congress of Military Medicine and Pharmacy at The Hague, Netherlands. There were ten United States delegates representing the U. S. Army, U. S. Navy, U. S. Public Health Service and the National Guard.

Dr. Fred M. F. Meixner (Fellow), Peoria, Ill., is the author of an article on "A Practical Classification of Heart Diseases," which appeared in the June, 1931, issue of the Peoria Medical News.

Dr. Harold G. F. Edwards (Fellow), Shreveport, La., is the author of an article on "A New Method for Studying Chest Films," appearing in the September, 1931, issue of Radiology.

At a regular meeting of the Fulton County Medical Society on September 3, a bust of the late Dr. Elmore Callaway Thrash (Fellow), of Atlanta, Ga., was unveiled in the library of the Academy of Medicine at Atlanta.

Dr. Horton Casparis (Fellow), Nashville, delivered a paper on "Allergy in Children" before the semi-annual meeting of the Southwestern Virginia Medical Society on September 24-25.

Dr. Francis H. Smith (Fellow), Abingdon, Va., also delivered a paper before the above meeting on "Coronary Disease as a Factor in Failing Myocardium."

Dr. Samuel E. Thompson (Fellow), Kerrville, Texas, was re-elected President

of the Southwest Texas District Medical Society at its semi-annual meeting on July 13-14.

Dr. Waller S. Leathers (Fellow), Dean, Vanderbilt University School of Medicine, Nashville, has been re-elected President of the National Board of Medical Examiners.

Dr. Luther C. Davis (Fellow), Fairmont, W. Va., has been appointed a member of the State Board of Nurses' Examiners to succeed the late Dr. Harry M. Hall (Fellow).

Dr. William E. Gardner (Fellow), Louisville, is Councilor for the Fifth District Medical Society, which was organized recently and is composed of physicians of Jefferson, Carroll, Trimble, Gallatin, Owen and Henry Counties (Kentucky). The new Society will meet twice a year.

The following Fellows of the College were on the faculty of the Annual Summer Graduate Course at the Louisville City Hospital, held under the auspices of the Kentucky State Medical Association and the University of Louisville School of Medicine:

Dr. Virgil E. Simpson, Dr. Philip F. Barbour, and Dr. Emmet F. Horine, all of Louisville.

Dr. Frank N. Wilson (Fellow), Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor, presented four lectures on electrocardiographic studies, October 19-22, in a series held in the auditorium of Mount Sinai Hospital in connection with the graduate fortnight of the New York Academy of Medicine.

The following Fellows of the College were among guest speakers at the sixty-first annual meeting of the Colorado State Medical Society on September 15-17:

Dr. Fred M. Smith, Iowa City—"Clinical Manifestations and Treatment of Coronary Artery Disease;"

Dr. Henry S. Plummer, Rochester, Minn.—"Adenomatous and Exophthalmic Goiter."

Drs. Lorenz W. Frank (Fellow) and Clough T. Burnett (Fellow), both of Denver, took part in a symposium on the arthritides, which was presented at the above meeting.

The International Association of Industrial Accident Boards and Commissions held its eighteenth annual convention October 5-9 at Richmond, Va. There were two medical sessions on Wednesday, October 7; the one in the morning was held under the Chairmanship of Dr. G. H. Gehrmann (Fellow), Medical Director of the E. I. duPont de Nemours and Company, Inc., Wilmington, Del. The following Fellows of the College were speakers at the morning session, as indicated:

Dr. Henry Field Smyth, Philadelphia,—Should a Course in Industrial Medicine be Included in the Curriculum of Medical Schools?" This paper was discussed by Dr. J. Allison Hodges (Fellow), President of the Medical Society of Virginia;

Drs. J. Morrison Hutcheson, Richmond, and Francis H. Smith, Abingdon, discussed a paper entitled "Settlements as a Therapeutic Measure."

The following Fellows of the College were speakers at the afternoon session, as indicated:

Dr. R. Finley Gayle, Richmond, discussed a paper on the "Care and Treatment of Injured to Avoid Traumatic Neurosis;"

Drs. Warren T. Vaughan and Dean Cole, both of Richmond, together discussed a paper on the "Differential Diagnosis of Traumatic and Occupational Chemical Injuries."

The fourth Graduate Fortnight of the New York Academy of Medicine was held October 19-30 on the general subject of "Disorders of the Circulation." Among members of the College who participated on the program were:

Dr. Warfield T. Longcope (Fellow), Baltimore—"Syphilitic Aortitis;"

Dr. Lewis A. Conner (Fellow), New York City—"Pericarditis — Diagnosis and Medical Treatment;"

Dr. Alfred Stengel (Master), Philadelphia—"Relation of Heart Disease to Operations;"

Dr. Harlow Brooks (Fellow), New York City—"The Heart of an Athlete;"

Dr. William Sydney Thayer (Fellow), Baltimore—"Endocarditis."

Dr. Edward O. Otis (Fellow), Exeter, N. H., who has been Governor of the American College of Physicians for the State of New Hampshire for several years, was recently honored by a special meeting at the headquarters of the Boston Tuberculosis Association, commemorating the fiftieth anniversary of his service in the field of tuberculosis. Dr. Frederick T. Lord (Fellow), and Dr. John B. Hawes, 2d. (Fellow), were speakers. Dr. Otis is a former President of the National Tuberculosis Association, Honorary President of the Massachusetts Tuberculosis League and Professor Emeritus of Pulmonary Diseases and Climatology at Tufts College Medical School. He is eighty-three years of age, and still engaged in active work.

The Medical Society of Virginia held its sixty-second annual session at Roanoke, October 6-8, under the Presidency of Dr. J. Allison Hodges (Fellow), Richmond. The following Fellows participated, as indicated:

Dr. Warren T. Vaughan, Richmond—"Arthritis Treated as a Form of Bacterial Allergy;"

Dr. D. C. Wilson, University—"A Survey of Mental Disease in Virginia;"

Dr. Beverley R. Tucker, Richmond—"A Suggested Program of Mental Hygiene for Virginia;"

Dr. Walter B. Martin, Norfolk—"Value of the Hormone Test for Early Pregnancy;"

Dr. H. B. Mulholland, University—"Diabetes in Children and Young Adults;"

Dr. J. Morrison Hutcheson, Richmond—"Physical Factors in Coronary Occlusion;"

Dr. William B. Porter, Richmond—"Angina Pectoris Associated with Pernicious Anemia".

Dr. Edward C. Mason (Fellow), Oklahoma City, Okla., is the author of an article entitled "The Modern Treatment of Burns," appearing in the August issue of the Journal of the Oklahoma State Medical Association.

Dr. Lewis B. Flinn (Fellow), Wilmington, Del., is the first President of the Academy of Medicine of Delaware, recently organized.

The Medical Society of the State of Pennsylvania held its eighty-first annual session at Scranton, Pa., October 5-8, under the Presidency of Dr. Ross V. Patterson (Fellow), Philadelphia. Dr. Elmer H. Funk (Fellow), Philadelphia, as Chairman of the Committee on Scientific Work, presented the program. Dr. William H. Mayer (Fellow), Pittsburgh, was installed as the new President for the coming year.

Fellows of the College who offered papers are listed below:

Dr. Roy R. Snowden, Pittsburgh—"Report of a Case of Osteomalacia;"

Dr. George R. Minot, Boston—"The Treatment of Anemia;"

Dr. Sydney R. Miller, Baltimore—"Contemporary Fads and Fallacies, Therapeutic and Diagnostic, which Reflect Dangerous Professional Credulity;"

Dr. Henry K. Mohler, Philadelphia—"Auricular Fibrillation—an Analysis of 220 Cases;"

Dr. O. H. Perry Pepper, Philadelphia—"Malignant Hypertension Simulating Brain Tumor;"

Dr. Willis F. Manges, Philadelphia—"Pulmonary Disease as the Result of Nasal Accessory Sinus Infection;"

Dr. Louis Hamman, Baltimore—"The Diagnosis of Obscure Fever;"

Dr. Charles C. Wolferth, Philadelphia—"Indications for the Use of Laboratory Methods of Cardiovascular Diagnosis;"

Dr. Edward L. Bortz, Philadelphia—Diffuse Gastric Hemorrhage with Special Reference to Dieulafoy's Ulcer;"

Dr. Edgar M. Green, Easton—"General Atelectasis of the Right Lung with the Heart Displaced to the Right of the Median Line and Left-Sided Pneumothorax;"

Dr. John D. Wilson, Scranton—"A Case of Xanthomatosis;"

Dr. George Morris Piersol, Philadelphia—"Granulopenia;"

Dr. Thomas Fitz-Hugh, Jr., Philadelphia—Leukemoid Blood Reactions;"

Dr. David Riesman, Philadelphia—"The Preoperative and Postoperative Treatmen of Surgical Diseases of the Kidney from the Medical Standpoint;"

Dr. E. Bosworth McCready, Pittsburgh—Relation of Endocrines to Juvenile Psychoses".

Dr. Orlando H. Petty (Fellow), Philadelphia, has been appointed Director of Public Health of the City of Philadelphia to fill out the term of Dr. Andrew Carns, recently deceased.

Dr. Beaumont S. Cornell (Fellow), Fort Wayne, Ind., addressed the eighty-second annual session of the Indiana State Medical Association, which was held at Indianapolis, September 23-25, on "Critical Review of Hypertension".

Dr. Roscoe L. Sensenich (Fellow), South Bend, Ind., participated in a symposium of gastro-intestinal diseases.

Dr. Waller S. Leathers (Fellow), Nashville, was among the speakers at a conference of public health workers of Kentucky, Tennessee and Missouri, held at Reelfoot Lake, Ky., August 21. Dr. Leathers' subject was "Preventive Medicine and its Relation to Public Health."

Drs. Wardner D. Ayer (Fellow), Syracuse, and Clayton W. Greene (Fellow), Buffalo, are members of a Committee on Infantile Paralysis appointed by the President of the Medical Society of the State of New York to assist the Chairman of the Standing Committee on Public Health in devising means by which family physicians may aid in the control of the present epidemic.

Dr. Lewis J. Morrman (Fellow), Oklahoma City, was appointed Dean of the University of Oklahoma School of Medicine.

The thirty-seventh annual meeting of the Utah State Medical Association was held at Salt Lake City, September 9-11, under the Presidency of Dr. William L. Rich (Fellow). The following members of the College appeared on the program:

Dr. William C. MacCarthy (Fellow), Rochester, Minn.—"Why Cancer is so Frequently Hopeless;"

Dr. Walter E. Leonard (Associate), Los Angeles, Calif.—"The Surgical Diabetic."

Dr. Julius H. Hess (Fellow), Chicago, addressed the American Dietetic Association, held at Cincinnati, October 19-21, on "Infant Feeding".

Drs. Noble Wiley Jones (Fellow), Portland, and Ralph C. Maston (Fellow), Portland, addressed the Idaho State Medical Association's meeting on "Chronic Sinus Infection in Relation to Systemic Disease" and "Treatment of Empyema," respectively.

Dr. Frederick Tice (Fellow), Chicago, was recently appointed President of the Board of Directors of the Municipal Tuberculosis Sanitarium.

Dr. Walter M. Simpson (Fellow), Dayton, and Dr. Paul A. O'Leary (Fellow), Rochester, Minn., delivered addresses on "Undulant Fever (Brucelliasis)" and "Vis-

ceral Syphilis", respectively, before the one hundred and eleventh meeting of the Michigan State Medical Society, held at Pontiac, September 22-24.

The following Fellows of the College were among the guest speakers at the all-day session of the Northwestern Ohio Medical Association, Marion, Ohio, October 6:

Dr. Nathan S. Davis, III, Chicago—"Cardiac Infarction without Pain;"

Dr. Julius H. Hess, Chicago—"A Study of Premature Infants."

Acknowledgment is made of the following gifts of reprints by members to the College Library:

Dr. Miles J. Breuer (Fellow), Lincoln, Neb.—1 reprint;

Dr. A. B. Brower (Fellow), Dayton, Ohio—1 reprint (with Dr. Walter M. Simpson (Fellow), Dayton, Ohio);

Dr. Robert Chobot (Fellow), New York, N. Y.—1 reprint;

Dr. A. Morris Ginsberg (Fellow), Kansas City, Mo.—1 reprint;

Dr. George B. Lake (Associate), Highland Park, Ill.—14 reprints.

OBITUARIES

DR. LEONARD M. MURRAY

Dr. Leonard M. Murray died suddenly at his home in Toronto, Saturday, August 8, 1931, under tragic circumstances. His family was abroad and unable to reach Toronto in time for the funeral which was held Thursday, August 13.

Dr. Murray was born in Truro, Nova Scotia, 1875. He graduated from McGill University Faculty of Medicine in 1900. He was sometime Provincial Pathologist of Nova Scotia and Professor of Pathology, Halifax Medical College; later Attending Physician, Halifax Children's Hospital and Professor of Medicine, Dalhousie University (Halifax). He served overseas during the War, at first in France and later at Bushy Park, England, the Canadian Hospital for cardiovascular cases. In 1919 he came to Toronto as Consultant in Diseases of the Cardiovascular System, for what is now known as the Federal Department of Pensions and National Health. He was appointed to the Department of Medicine, University of Toronto, and to the Staff of the Toronto General Hospital for the years 1919 to 1928, when he resigned largely on account of the pressure of work due to private practice and the departmental work at Christie Street Hospital.

During his professional life he did postgraduate work in England, the United States, and abroad. He was a Fellow of the American College of Physicians and served on the Board of Regents for many years. He was elected a Fellow of the recently formed Royal College of Physicians and Surgeons of Canada in 1931. At the time of his death he was, in addition, a member of the Toronto Academy of Medicine, the Ontario and Canadian Medical Societies, the American Therapeutic Association and the Association for the Study of Internal Secretions. His later publications dealt entirely with diseases of the cardio-vascular system.

The above is but a brief outline of his professional career. His advent to Toronto was a happy one for those of his friends who lived here. Strong bands of esteem and affection quickly were formed, not only amongst the members of the medical profession but

as well amongst those who sought his advice and all who came in contact with him. There are those, not necessarily classed as cynics, who regard this as a real accomplishment. He was a member of The York Club and The Lambton Golf Club.

Saturday, August 8, was warm. Dr. Murray had planned a fairly full day, which was begun by meeting two distinguished guests at the station early in the morning. This was followed by a foursome at golf during which he played a good game. That he nevertheless felt under some distress is evidenced by the fact that he took an early morning mixture of soda bicarbonate, repeating this after his return to his house in the early afternoon. He apparently refused to do more than rest for a short time before again driving to the hospital to see a patient. After his return from the hospital, he was in evident distress and to those of us who have learned his philosophical outlook on life, it is evident that he more than suspected his real condition. This time he took a stimulant but shortly after insisted upon receiving his guests who had been elsewhere for tea. As all were tired and the day hot, a short rest was welcomed before dressing for a dinner which was to take place later at The York Club. The chance call of one of the guests as to the time of dinner led to the discovery of his collapse and death but a few moments after he had seen that his house guests were comfortable. In the crucial few hours before his death, and while under distress, philosophy rather than medical judgment guided his actions—to the bitter sorrow of many. The diagnosis would seem to be coronary thrombosis.

It is of professional interest to record that four electro-cardiographs had been taken, the last being in February, 1931. In his own phraseology, these fell within the accepted normal, except for a slight left ventricular preponderance. A more definite indication is given in that but a few days previously, in talking over the effect of golf on hot days with one of his colleagues, a slight amount of discomfort was mentioned.

In the delicious intimacy of an evening's relaxation amongst a few friends, which he so thoroughly enjoyed, Dr. Murray had more than once declared that when he "went" he hoped he would go quickly, that he would be buried without "fuss or fumble" and "be forgotten." The first part of this wish has been fulfilled; the last, for his colleagues, for those who sought his advice or held his friendship, is impossible. His personality, charm, humor, sympathy and ability will in their memory endure for all time.

(Furnished by A. H. W. Caulfeild, M.D., F.A.C.P., Toronto.)

DOCTOR ELMORE CALLAWAY THRASH

Dr. Elmore Callaway Thrash (Fellow) died at Boulder Crest, Atlanta, Ga., on June 22, 1931, in his sixty-fifth year. Although the end came suddenly, it was not unexpected, as six months before he had developed a partial occlusion of a coronary artery. As an evidence of his devotion to duty and of his loyalty to his friends, shortly before his death he

attended the recent meeting of the American Medical Association as a member of the House of Delegates in order to serve as the representative of the medical profession of Georgia. On his return he was confined to his home up to the time of his death.

Dr. Thrash was born in Meriwether County, Georgia, on February 20, 1867. He was graduated with honors from the University of Louisville School of Medicine in 1891. He served as president of the Fulton County Medical Society and also the Medical Association of Georgia. In his early life Dr. Thrash read a paper before the Medical Association of Georgia urging the establishment of a State Board of Health. This attracted so much attention that it was published in pamphlet form and distributed among the voters of the State. Soon after this the very efficient Georgia State Board of Health was organized.

In 1905 Dr. Thrash was elected Professor of Pathology and Bacteriology in the Atlanta School of Medicine and he served in this capacity until 1914, in which year he was elected Professor of Diseases of the Chest in the Atlanta Medical College.

Dr. Thrash always took a leading part in the various activities of the local, state and national medical associations. At these meetings he always stood for what was right, even if he stood alone. He read numerous papers dealing with pathology, bacteriology and internal medicine before medical societies throughout the nation and his views always commanded attention. Being a fluent speaker, having an alert mind, and a distinguished personality—which was unforgettable—he was probably better known than any other physician in the South.

On September 3, 1931, the medical profession of Atlanta presented to the Library of the Fulton County Medical Society a marble portrait bust of Dr. Thrash as a tribute to his services to the medical profession and to mankind.

(Furnished by Jas. N. Brawner, M. D., Atlanta, Ga.)

DOCTOR (LT. COL.) WILLIAM STEPHENS SHIELDS

Lt. Col. William Stephens Shields (Fellow), Medical Corps, U. S. Army, died, August 6, 1931, at the Letterman General Hospital, San Francisco, after an illness of about a year; aged 49 years.

Lt. Col. Shields was born at Washington, Georgia, and after completing his preliminary education, attended the Medico-Chirurgical College at Philadelphia, from which he received the degree of M. D. in 1906. He pursued postgraduate study at the Army Medical School and Columbia University, and was later a Fellow in Medicine under the Mayo Foundation. He was the author of a number of publications appearing in the Military Surgeon. He was a Fellow of the American Medical Association, and was elected a Fellow of the American College of Physicians on November 17, 1928.

DR. HENRY LYLE WINTER

Dr. Henry Lyle Winter (Fellow), Newburgh, N. Y., died of heart disease, July 29, 1931; aged 63 years.

Dr. Winter was born in Brooklyn, July 7, 1868, attended Brooklyn High School and later received his medical degree from New York University in 1892. He pursued postgraduate study in Munich, Nancy and Paris. He formerly held appointments as instructor in neurology at the University and Bellevue Hospital Medical College, associate in anthropology at the Pathological Institute of the New York State Hospitals for the Insane, and attending neurologist at the University and Bellevue Clinic. Dr. Winter served during the World War; he was formerly president of the Board of Education of Cornwall. At the time of his death, he was consulting neurologist to Cornwall and St. Luke's Hospitals.

Dr. Winter was ex-vice president and ex-president of the Orange County Medical Society, a member of the Medical Society of the State of New York, a Fellow of the American Medical Association, and a member of the American Association for the Advancement of Science. He had been a Fellow of the American College of Physicians since April 10, 1917. He was the author of many articles, published in leading medical journals.

DR. EDWARD P. SCHATZMAN

Dr. Edward P. Schatzman (Associate), Pittsburgh, Pa., died July 27, 1931, of heart disease; aged 55 years. Dr. Schatzman was a graduate of Western Pennsylvania Medical College, Pittsburgh, in 1900. He was a member of the Nu Sigma Nu Fraternity, Allegheny County Medical Society, Pennsylvania State Medical Association, and the American Medical Association. He had been an Associate of the American College of Physicians since April 3, 1923. His practice had long been limited to internal medicine and diagnosis.

DR. JOSEPH WITHAM YOUNG

Dr. Joseph Witham Young (Associate), Toledo, Ohio, died July 14, 1931; aged 54 years.

Dr. Young received his B.S. degree from Cornell University in 1899, and his M.D. degree from Columbia University College of Physicians and Surgeons, 1903. From 1905 to 1906, he did postgraduate study in pathology and in internal medicine at the University of Berlin, and during 1919 in internal medicine at Harvard University Medical School. From 1906 to 1911, Dr. Young resided in New York City, where he was assistant to the Out-patient Department of Bellevue Hospital and assistant in the Medical Department of the Vanderbilt Clinic. He had been a member of the staff of the Robinwood Hospital of Toledo since 1918.

Dr. Young was a member of the Phi Delta Theta medical fraternity, a member and ex-chairman of the medical section of the Academy of Medicine of Toledo, a member of the Ohio State Medical Association, Northern Tri-State Medical Association, Northwestern Ohio Medical Association, and a Fellow of the American Medical Association. He had been an Associate of the American College of Physicians since April 3, 1922.